

# Application of a next generation risk assessment framework for skin sensitisation using new approach methodologies (NAMs)

Renato Ivan de Ávila, PhD

Scientist – Human Safety

Unilever Safety and Environmental Assurance Centre (SEAC)

## WEBINAR

Métodos Alternativos ao uso de animais para indústria de Higiene Pessoal, Perfumaria e Cosméticos



Unilever

# Agenda

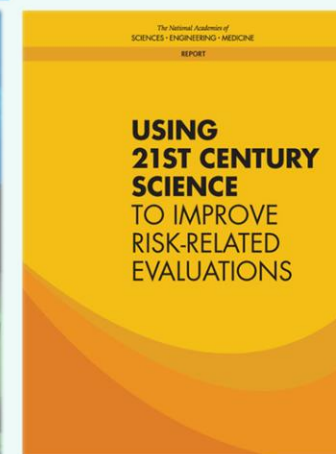
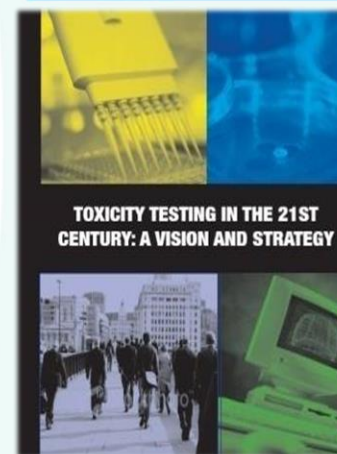
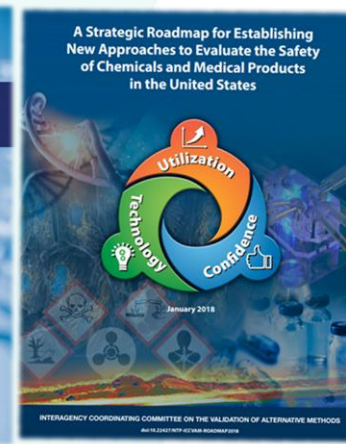
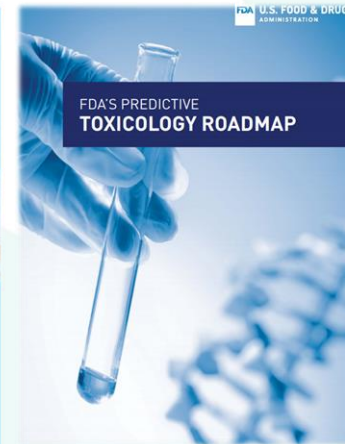
1. Assessing ingredient & product safety without animal testing
2. Skin allergy risk assessment evolution
3. Use of Skin Sensitisation Adverse Outcome Pathway (AOP) to develop NAMs
4. Next generation risk assessment (NGRA) framework for skin allergy
5. Skin allergy Risk Assessment (SARA) model
6. Case study: 0.02% (200ppm) geraniol in a face cream
7. Conclusions & Next Steps

# Assessing ingredient & product safety without animal testing

## Next Generation Risk Assessment (NGRA)

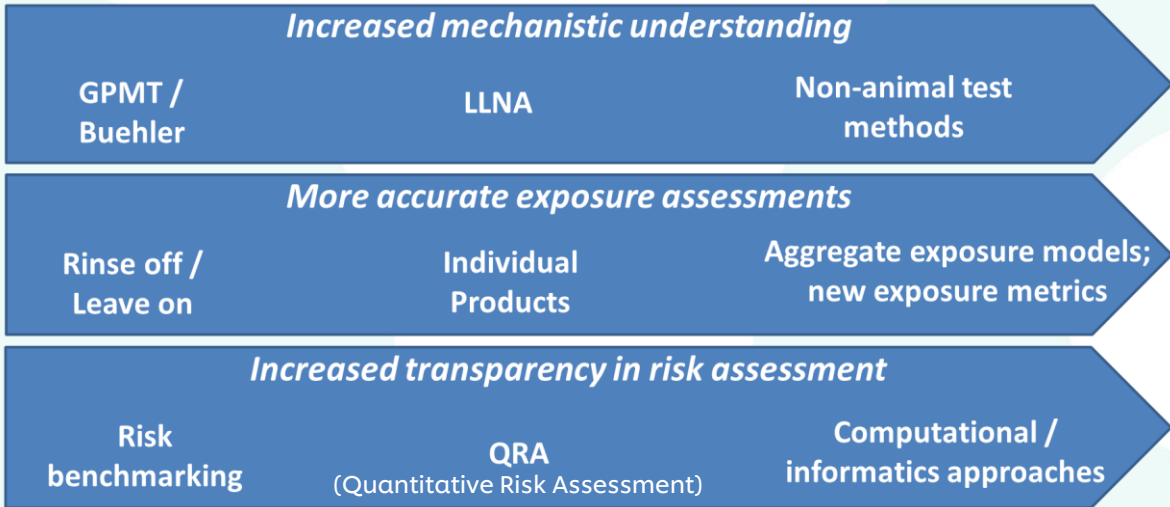


Is it safe to include x% of chemical y in product z?





# Skin allergy risk assessment evolution



Section 4  
Health effects

Guideline No. 497  
Guideline on Defined Approaches for Skin Sensitisation

14 June 2021

OECD Guidelines for the Testing of Chemicals

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)  
**ScienceDirect**  
 Regulatory Toxicology and Pharmacology 52 (2018) 3–23  
[www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

**Regulatory Toxicology and Pharmacology**

### Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients

Anne Marie Api <sup>a,\*</sup>, David A. Basketter <sup>b,c</sup>, Peter A. Cadby <sup>d</sup>, Marie-France Cano <sup>d,2</sup>, Graham Ellis <sup>e</sup>, G. Frank Gerberick <sup>f</sup>, Peter Griem <sup>g</sup>, Pauline M. McNamee <sup>h</sup>, Cindy A. Ryan <sup>i</sup>, Robert Safford <sup>h</sup>

<sup>a</sup> Research Institute for Fragrance Materials, Inc., 50 The Boulevard, Woodbridge, NJ, USA  
<sup>b</sup> Institute SCAI, Colson House, Sherbrooke, Bedford MK44 1JG, United Kingdom  
<sup>c</sup> Financière SA, Corporate Product Safety & Regulatory Affairs, Case postale 219, 1, Route de Janelle à Janelle, Geneva 8 CH-1211, Switzerland  
<sup>d</sup> IFAH, Fragrance Safety and Regulatory Affairs, 157 Avenue de Verdun, Saint Jean de Braye Cedex F-41084, France  
<sup>e</sup> GlaxoSmithKline SA, 5 Avenue de la Performance, Vernier CH-1214, Switzerland  
<sup>f</sup> The Procter & Gamble Company, Miami Valley Laboratories, 1130 East Miami River Road, Cincinnati, OH 45222, USA  
<sup>g</sup> Clariant Products (Netherlands) GmbH, Corporate Product Safety, Am Engey Park 1, 63644 Seltzheim, Germany  
<sup>h</sup> The Procter & Gamble Technical Center Ltd, Whitehall Lane, Egham Surrey TW20 9NW, United Kingdom  
<sup>i</sup> L'Oréal, 23 Avenue de France, Paris, France

Received 16 July 2017  
 Available online 24 October 2017

**Abstract**

Based on chemical, cellular, and molecular understanding of dermal sensitization, an exposure-based quantitative risk assessment (QRA) can be conducted to determine safe use levels of fragrance ingredients in different consumer product types. The key steps are: (1) identification of chemicals, (2) calculation of dermal sensitization induction level (NSIL), (3) application of sensitization assessment factors (SAF), and (4) consumer exposure (CE) calculation through product use. Using these parameters, an acceptable exposure level (AEL) can be calculated and compared with the CE. The ratio of AEL to CE must be favorable to support safe use of the potential skin sensitizer. This ratio must be calculated for the fragrance ingredient in each product type. Based on the Research Institute for Fragrance Materials, Inc. (RIFM) Expert Panel's recommendation, RIFM and the International Fragrance Association (IFA) have adopted the dermal sensitization QRA approach described in this review for fragrance ingredients identified as potential dermal sensitizers. This new form the fragrance industry's core strategy for primary prevention of dermal sensitization to these materials in consumer products. This methodology is used to determine global fragrance industry product management practices (IFA Standards) for fragrance ingredients that are potential dermal sensitizers. This paper describes the principles of the recommended approach, provides detailed review of all the information used in the dermal sensitization QRA approach for fragrance ingredients and presents key conclusions for its use now and refinement in the future.

**Keywords:** Quantitative risk assessment, Dermal sensitization, Fragrance ingredients, NSIL, SAF, AEL, CEI.

**1. Introduction**

Although some substances in common use today may have the potential to cause dermal sensitization, they can be formulated into consumer products at safe levels. This is also the case for fragrance ingredients.

IFA provides the fragrance industry with risk management strategies on the use of fragrance ingredients includ-

Regulatory Toxicology and Pharmacology 118 (2020) 104458

Contents lists available at [ScienceDirect](http://ScienceDirect)  
**Regulatory Toxicology and Pharmacology**  
[journal homepage: www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

### Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials

Anne Marie Api <sup>a,\*</sup>, David Basketter <sup>b,c</sup>, James Bridges <sup>d</sup>, Peter Cadby <sup>e</sup>, Graham Ellis <sup>f</sup>, Nicola Gilmour <sup>g</sup>, Helmut Geism <sup>h</sup>, Peter Griem <sup>i</sup>, Petra Kern <sup>j</sup>, Alain Khayat <sup>k</sup>, John O'Brien <sup>l</sup>, Thomas Rutenmeyer <sup>m</sup>, Cindy Ryan <sup>n</sup>, Bob Safford <sup>o</sup>, Benjamin Smith <sup>n,2</sup>, Matthias Vey <sup>o</sup>, Jan R. Vliet <sup>o</sup>

<sup>a</sup> Research Institute for Fragrance Materials, Inc., 50 The Boulevard, Woodbridge, NJ, USA  
<sup>b</sup> Institute SCAI, Colson House, Sherbrooke, Bedford MK44 1JG, United Kingdom  
<sup>c</sup> Financière SA, Corporate Product Safety & Regulatory Affairs, Case postale 219, 1, Route de Janelle à Janelle, Geneva 8 CH-1211, Switzerland  
<sup>d</sup> IFAH, Fragrance Safety and Regulatory Affairs, 157 Avenue de Verdun, Saint Jean de Braye Cedex F-41084, France  
<sup>e</sup> GlaxoSmithKline SA, 5 Avenue de la Performance, Vernier CH-1214, Switzerland  
<sup>f</sup> The Procter & Gamble Company, Miami Valley Laboratories, 1130 East Miami River Road, Cincinnati, OH 45222, USA  
<sup>g</sup> Clariant Products (Netherlands) GmbH, Corporate Product Safety, Am Engey Park 1, 63644 Seltzheim, Germany  
<sup>h</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>i</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>j</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>k</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>l</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>m</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>n</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>o</sup> L'Oréal, 23 Avenue de France, Paris, France

Received 16 July 2017  
 Available online 24 October 2017

**Abstract**

Based on chemical, cellular, and molecular understanding of dermal sensitization, an exposure-based quantitative risk assessment (QRA) can be conducted to determine safe use levels of fragrance ingredients in different consumer product types. The key steps are: (1) identification of chemicals, (2) calculation of dermal sensitization induction level (NSIL), (3) application of sensitization assessment factors (SAF), and (4) consumer exposure (CE) calculation through product use. Using these parameters, an acceptable exposure level (AEL) can be calculated and compared with the CE. The ratio of AEL to CE must be favorable to support safe use of the potential skin sensitizer. This ratio must be calculated for the fragrance ingredient in each product type. Based on the Research Institute for Fragrance Materials, Inc. (RIFM) Expert Panel's recommendation, RIFM and the International Fragrance Association (IFA) have adopted the dermal sensitization QRA approach described in this review for fragrance ingredients identified as potential dermal sensitizers. This new form the fragrance industry's core strategy for primary prevention of dermal sensitization to these materials in consumer products. This methodology is used to determine global fragrance industry product management practices (IFA Standards) for fragrance ingredients that are potential dermal sensitizers. This paper describes the principles of the recommended approach, provides detailed review of all the information used in the dermal sensitization QRA approach for fragrance ingredients and presents key conclusions for its use now and refinement in the future.

**Keywords:** Quantitative risk assessment, Dermal sensitization, Fragrance ingredients, NSIL, SAF, AEL, CEI.

**1. Introduction**

Although some substances in common use today may have the potential to cause dermal sensitization, they can be formulated into consumer products at safe levels. This is also the case for fragrance ingredients.

IFA provides the fragrance industry with risk management strategies on the use of fragrance ingredients includ-

Regulatory Toxicology and Pharmacology 116 (2020) 104721

Contents lists available at [ScienceDirect](http://ScienceDirect)  
**Regulatory Toxicology and Pharmacology**  
[journal homepage: www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

### Development of a next generation risk assessment framework for the evaluation of skin sensitisation of cosmetic ingredients

Nicola Gilmour <sup>a,1</sup>, Petra S. Kern <sup>b,1</sup>, Nathalie Alépée <sup>c</sup>, Fanny Boislevé <sup>d</sup>, Dagmar Bury <sup>e</sup>, Elodie Clouet <sup>f</sup>, Morihiko Hirota <sup>g</sup>, Sebastian Hoffmann <sup>h</sup>, Jochen Kühnl <sup>i</sup>, Jon F. Lalko <sup>j</sup>, Karenn Meves <sup>k</sup>, Masaki Miyazawa <sup>l</sup>, Hayato Nishida <sup>m</sup>, Anne Osman <sup>n</sup>, Dirk Petersohn <sup>o</sup>, Shuichi Sekine <sup>p</sup>, Erwin van Vliet <sup>q</sup>, Martina Klaric <sup>r</sup>

<sup>a</sup> Institut Cosmétologie Sciences Paris, Institut IMC, 8414 010, United Kingdom  
<sup>b</sup> Procter & Gamble Services NV/SA, Formulation, Beerselhoven, 1815, Struelensdreef, Belgium  
<sup>c</sup> L'Oréal, Research & Innovation, Adress-vent-Arde, Cléry, France  
<sup>d</sup> Clouet, 127 Avenue Charles de Gaulle, 92221, Nanterre, France  
<sup>e</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>f</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>g</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>h</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>i</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>j</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>k</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>l</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>m</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>n</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>o</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>p</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>q</sup> L'Oréal, 23 Avenue de France, Paris, France  
<sup>r</sup> L'Oréal, 23 Avenue de France, Paris, France

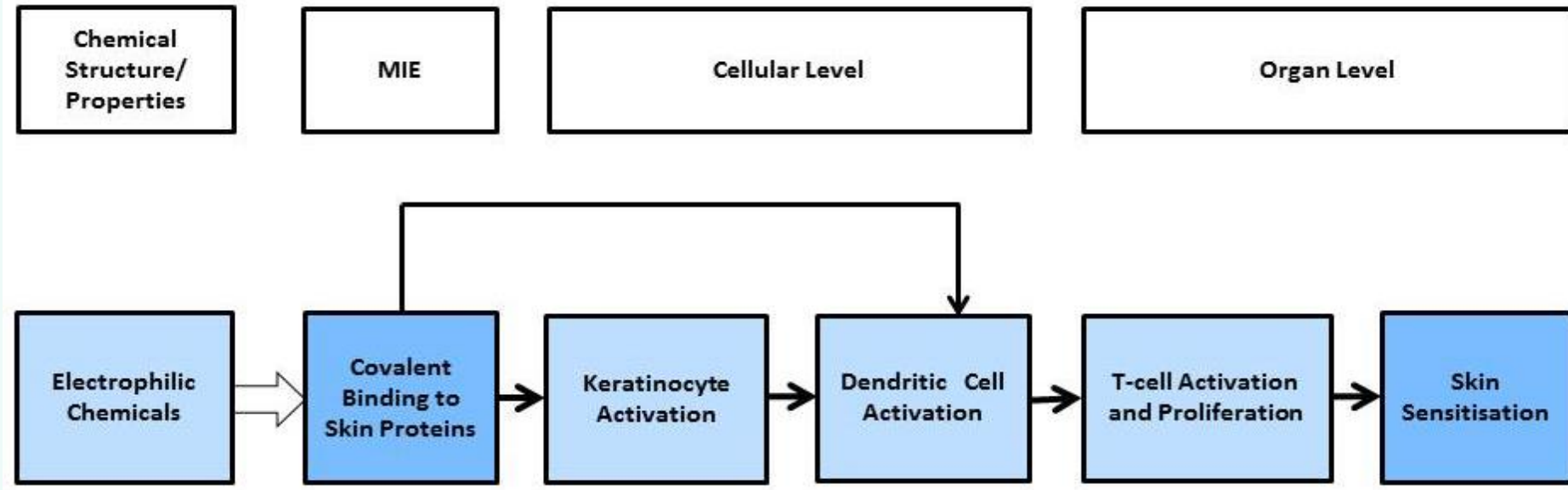
Received 16 July 2017  
 Available online 24 October 2017

**Abstract**

All cosmetic products placed on the market must undergo a risk assessment for human health to ensure they are safe for consumers, including an assessment of skin sensitisation risk. Historically, in vivo animal test methods were used to identify and characterise skin sensitisation hazard, however non-animal and other new approach methodologies (NAMs) are now preferred and mandated choice for use in risk assessment for cosmetic ingredients. The experience gained over the last three decades on how to conduct risk assessments based upon NAMs has allowed us to develop a non-animal, non-proprietary risk assessment (NORA) framework for the assessment of skin sensitisation. The framework presented here is based upon the principles published by the International Cooperation on Cosmetic Regulation (ICCCR) and is human relevant, exposure-led, hypothesis-driven and designed to prevent harm. It is structured in three tiers and integrates and refines information using a weight of evidence (WoE) approach that can be tailored where new information becomes available. The initial tier (ITER 1) involves a thorough review of the existing information including: identification of the use scenario/consumer exposure; characterisation of the chemical entity and structure; and relevant information relating data pertaining to skin sensitisation hazard (intrinsic or non-intrinsic), the identification of suitable read-across conditions with supporting hazard identification characterisation information and application of exposure-based metrics. Considering all information identified in ITER 1, the next step in the progression of a hypothesis (ITER 1). All data are considered in an exposure-led WoE approach, taking into account an initial view on whether a chemical is likely to be a skin sensitizer or not, based on defined approach (DA) and availability of read-across conditions. If existing information is insufficient for concluding the risk assessment, the generation of additional information may be required to proceed (ITER 2). Such targeted testing could involve refinement of the exposure estimation or generation of data from in vivo or in chemico NAMs, their sufficient information is available, the final stage of the NORA framework is the determination of a point of departure (POD), characterising uncertainty and comparing to the consumer exposure in a WoE. Through evaluation of the measures of uncertainty it is possible to ensure transparency and build trust in new risk assessment approaches. Although significant progress has been made, industry must continue to invest in research to skin sensitisation NORA to ensure that it can be used to demonstrate that this new risk assessment approach is protective for consumers. Dialogue and collaboration between key stakeholders, i.e. risk assessors, clinicians and regulators are important to gain mutual understanding and grow confidence in new approaches.

**Keywords:** Skin sensitisation, NAMs, WoE, NORA, ITER 1, ITER 2, ITER 3, ITER 4, ITER 5, ITER 6, ITER 7, ITER 8, ITER 9, ITER 10, ITER 11, ITER 12, ITER 13, ITER 14, ITER 15, ITER 16, ITER 17, ITER 18, ITER 19, ITER 20, ITER 21, ITER 22, ITER 23, ITER 24, ITER 25, ITER 26, ITER 27, ITER 28, ITER 29, ITER 30, ITER 31, ITER 32, ITER 33, ITER 34, ITER 35, ITER 36, ITER 37, ITER 38, ITER 39, ITER 40, ITER 41, ITER 42, ITER 43, ITER 44, ITER 45, ITER 46, ITER 47, ITER 48, ITER 49, ITER 50, ITER 51, ITER 52, ITER 53, ITER 54, ITER 55, ITER 56, ITER 57, ITER 58, ITER 59, ITER 60, ITER 61, ITER 62, ITER 63, ITER 64, ITER 65, ITER 66, ITER 67, ITER 68, ITER 69, ITER 70, ITER 71, ITER 72, ITER 73, ITER 74, ITER 75, ITER 76, ITER 77, ITER 78, ITER 79, ITER 80, ITER 81, ITER 82, ITER 83, ITER 84, ITER 85, ITER 86, ITER 87, ITER 88, ITER 89, ITER 90, ITER 91, ITER 92, ITER 93, ITER 94, ITER 95, ITER 96, ITER 97, ITER 98, ITER 99, ITER 100, ITER 101, ITER 102, ITER 103, ITER 104, ITER 105, ITER 106, ITER 107, ITER 108, ITER 109, ITER 110, ITER 111, ITER 112, ITER 113, ITER 114, ITER 115, ITER 116, ITER 117, ITER 118, ITER 119, ITER 120, ITER 121, ITER 122, ITER 123, ITER 124, ITER 125, ITER 126, ITER 127, ITER 128, ITER 129, ITER 130, ITER 131, ITER 132, ITER 133, ITER 134, ITER 135, ITER 136, ITER 137, ITER 138, ITER 139, ITER 140, ITER 141, ITER 142, ITER 143, ITER 144, ITER 145, ITER 146, ITER 147, ITER 148, ITER 149, ITER 150, ITER 151, ITER 152, ITER 153, ITER 154, ITER 155, ITER 156, ITER 157, ITER 158, ITER 159, ITER 160, ITER 161, ITER 162, ITER 163, ITER 164, ITER 165, ITER 166, ITER 167, ITER 168, ITER 169, ITER 170, ITER 171, ITER 172, ITER 173, ITER 174, ITER 175, ITER 176, ITER 177, ITER 178, ITER 179, ITER 180, ITER 181, ITER 182, ITER 183, ITER 184, ITER 185, ITER 186, ITER 187, ITER 188, ITER 189, ITER 190, ITER 191, ITER 192, ITER 193, ITER 194, ITER 195, ITER 196, ITER 197, ITER 198, ITER 199, ITER 200, ITER 201, ITER 202, ITER 203, ITER 204, ITER 205, ITER 206, ITER 207, ITER 208, ITER 209, ITER 210, ITER 211, ITER 212, ITER 213, ITER 214, ITER 215, ITER 216, ITER 217, ITER 218, ITER 219, ITER 220, ITER 221, ITER 222, ITER 223, ITER 224, ITER 225, ITER 226, ITER 227, ITER 228, ITER 229, ITER 230, ITER 231, ITER 232, ITER 233, ITER 234, ITER 235, ITER 236, ITER 237, ITER 238, ITER 239, ITER 240, ITER 241, ITER 242, ITER 243, ITER 244, ITER 245, ITER 246, ITER 247, ITER 248, ITER 249, ITER 250, ITER 251, ITER 252, ITER 253, ITER 254, ITER 255, ITER 256, ITER 257, ITER 258, ITER 259, ITER 260, ITER 261, ITER 262, ITER 263, ITER 264, ITER 265, ITER 266, ITER 267, ITER 268, ITER 269, ITER 270, ITER 271, ITER 272, ITER 273, ITER 274, ITER 275, ITER 276, ITER 277, ITER 278, ITER 279, ITER 280, ITER 281, ITER 282, ITER 283, ITER 284, ITER 285, ITER 286, ITER 287, ITER 288, ITER 289, ITER 290, ITER 291, ITER 292, ITER 293, ITER 294, ITER 295, ITER 296, ITER 297, ITER 298, ITER 299, ITER 300, ITER 301, ITER 302, ITER 303, ITER 304, ITER 305, ITER 306, ITER 307, ITER 308, ITER 309, ITER 310, ITER 311, ITER 312, ITER 313, ITER 314, ITER 315, ITER 316, ITER 317, ITER 318, ITER 319, ITER 320, ITER 321, ITER 322, ITER 323, ITER 324, ITER 325, ITER 326, ITER 327, ITER 328, ITER 329, ITER 330, ITER 331, ITER 332, ITER 333, ITER 334, ITER 335, ITER 336, ITER 337, ITER 338, ITER 339, ITER 340, ITER 341, ITER 342, ITER 343, ITER 344, ITER 345, ITER 346, ITER 347, ITER 348, ITER 349, ITER 350, ITER 351, ITER 352, ITER 353, ITER 354, ITER 355, ITER 356, ITER 357, ITER 358, ITER 359, ITER 360, ITER 361, ITER 362, ITER 363, ITER 364, ITER 365, ITER 366, ITER 367, ITER 368, ITER 369, ITER 370, ITER 371, ITER 372, ITER 373, ITER 374, ITER 375, ITER 376, ITER 377, ITER 378, ITER 379, ITER 380, ITER 381, ITER 382, ITER 383, ITER 384, ITER 385, ITER 386, ITER 387, ITER 388, ITER 389, ITER 390, ITER 391, ITER 392, ITER 393, ITER 394, ITER 395, ITER 396, ITER 397, ITER 398, ITER 399, ITER 400, ITER 401, ITER 402, ITER 403, ITER 404, ITER 405, ITER 406, ITER 407, ITER 408, ITER 409, ITER 410, ITER 411, ITER 412, ITER 413, ITER 414, ITER 415, ITER 416, ITER 417, ITER 418, ITER 419, ITER 420, ITER 421, ITER 422, ITER 423, ITER 424, ITER 425, ITER 426, ITER 427, ITER 428, ITER 429, ITER 430, ITER 431, ITER 432, ITER 433, ITER 434, ITER 435, ITER 436, ITER 437, ITER 438, ITER 439, ITER 440, ITER 441, ITER 442, ITER 443, ITER 444, ITER 445, ITER 446, ITER 447, ITER 448, ITER 449, ITER 450, ITER 451, ITER 452, ITER 453, ITER 454, ITER 455, ITER 456, ITER 457, ITER 458, ITER 459, ITER 460, ITER 461, ITER 462, ITER 463, ITER 464, ITER 465, ITER 466, ITER 467, ITER 468, ITER 469, ITER 470, ITER 471, ITER 472, ITER 473, ITER 474, ITER 475, ITER 476, ITER 477, ITER 478, ITER 479, ITER 480, ITER 481, ITER 482, ITER 483, ITER 484, ITER 485, ITER 486, ITER 487, ITER 488, ITER 489, ITER 490, ITER 491, ITER 492, ITER 493, ITER 494, ITER 495, ITER 496, ITER 497, ITER 498, ITER 499, ITER 500, ITER 501, ITER 502, ITER 503, ITER 504, ITER 505, ITER 506, ITER 507, ITER 508, ITER 509, ITER 510, ITER 511, ITER 512, ITER 513, ITER 514, ITER 515, ITER 516, ITER 517, ITER 518, ITER 519, ITER 520, ITER 521, ITER 522, ITER 523, ITER 524, ITER 525, ITER 526, ITER 527, ITER 528, ITER 529, ITER 530, ITER 531, ITER 532, ITER 533, ITER 534, ITER 535, ITER 536, ITER 537, ITER 538, ITER 539, ITER 540, ITER 541, ITER 542, ITER 543, ITER 544, ITER 545, ITER 546, ITER 547, ITER 548, ITER 549, ITER 550, ITER 551, ITER 552, ITER 553, ITER 554, ITER 555, ITER 556, ITER 557, ITER 558, ITER 559, ITER 560, ITER 561, ITER 562, ITER 563, ITER 564, ITER 565, ITER 566, ITER 567, ITER 568, ITER 569, ITER 570, ITER 571, ITER 572, ITER 573, ITER 574, ITER 575, ITER 576, ITER 577, ITER 578, ITER 579, ITER 580, ITER 581, ITER 582, ITER 583, ITER 584, ITER 585, ITER 586, ITER 587, ITER 588, ITER 589, ITER 590, ITER 591, ITER 592, ITER 593, ITER 594, ITER 595, ITER 596, ITER 597, ITER 598, ITER 599, ITER 600, ITER 601, ITER 602, ITER 603, ITER 604, ITER 605, ITER 606, ITER 607, ITER 608, ITER 609, ITER 610, ITER 611, ITER 612, ITER 613, ITER 614, ITER 615, ITER 616, ITER 617, ITER 618, ITER 619, ITER 620, ITER 621, ITER 622, ITER 623, ITER 624, ITER 625, ITER 626, ITER 627, ITER 628, ITER 629, ITER 630, ITER 631, ITER 632, ITER 633, ITER 634, ITER 635, ITER 636, ITER 637, ITER 638, ITER 639, ITER 640, ITER 641, ITER 642, ITER 643, ITER 644, ITER 645, ITER 646, ITER 647, ITER 648, ITER 649, ITER 650, ITER 651, ITER 652, ITER 653, ITER 654, ITER 655, ITER 656, ITER 657, ITER 658, ITER 659, ITER 660, ITER 661, ITER 662, ITER 663, ITER 664, ITER 665, ITER 666, ITER 667, ITER 668, ITER 669, ITER 670, ITER 671, ITER 672, ITER 673, ITER 674, ITER 675, ITER 676, ITER 677, ITER 678, ITER 679, ITER 680, ITER 681, ITER 682, ITER 683, ITER 684, ITER 685, ITER 686, ITER 687, ITER 688, ITER 689, ITER 690, ITER 691, ITER 692, ITER 693, ITER 694, ITER 695, ITER 696, ITER 697, ITER 698, ITER 699, ITER 700, ITER 701, ITER 702, ITER 703, ITER 704, ITER 705, ITER 706, ITER 707, ITER 708, ITER 709, ITER 710, ITER 711, ITER 712, ITER 713, ITER 714, ITER 715, ITER 716, ITER 717, ITER 718, ITER 719, ITER 720, ITER 721, ITER 722, ITER 723, ITER 724, ITER 725, ITER 726, ITER 727, ITER 728, ITER 729, ITER 730, ITER 731, ITER 732, ITER 733, ITER 734, ITER 735, ITER 736, ITER 737, ITER 738, ITER 739, ITER 740, ITER 741, ITER 742, ITER 743, ITER 744, ITER 745, ITER 746, ITER 747, ITER 748, ITER 749, ITER 750, ITER 751, ITER 752, ITER 753, ITER 754, ITER 755, ITER 756, ITER 757, ITER 758, ITER 759, ITER 760, ITER 761, ITER 762, ITER 763, ITER 764, ITER 765, ITER 766, ITER 767, ITER 768, ITER 769, ITER 770, ITER 771, ITER 772, ITER 773, ITER 774, ITER 775, ITER 776, ITER 777, ITER 778, ITER 779, ITER 780, ITER 781, ITER 782, ITER 783, ITER 784, ITER 785, ITER 786, ITER 787, ITER 788, ITER 789, ITER 790, ITER 791, ITER 792, ITER 793, ITER 794, ITER 795, ITER 796, ITER 797, ITER 798, ITER 799, ITER 800, ITER 801, ITER 802, ITER 803, ITER 804, ITER 805, ITER 806, ITER 807, ITER 808, ITER 809, ITER 810, ITER 811, ITER 812, ITER 813, ITER 814, ITER 815, ITER 816, ITER 817, ITER 818, ITER 819, ITER 820, ITER 821, ITER 822, ITER 823, ITER 824, ITER 825, ITER 826, ITER 827, ITER 828, ITER 829, ITER 830, ITER 831, ITER 832, ITER 833, ITER 834, ITER 835, ITER 836, ITER 837, ITER 838, ITER 839, ITER 840, ITER 841, ITER 842, ITER 843, ITER 844, ITER 845, ITER 846, ITER 847, ITER 848, ITER 849, ITER 850, ITER 851, ITER 852, ITER 853, ITER 854, ITER 855, ITER 856, ITER 857, ITER 858, ITER 859, ITER 860, ITER 861, ITER 862, ITER 863, ITER 864, ITER 865, ITER 866, ITER 867, ITER 868, ITER 869, ITER 870, ITER 871, ITER 872, ITER 873, ITER 874, ITER 875, ITER 876, ITER 877, ITER 878, ITER 879, ITER 880, ITER 881, ITER 882, ITER 883, ITER 884, ITER 885, ITER 886, ITER 887, ITER 888, ITER 889, ITER 890, ITER 891, ITER 892, ITER 893, ITER 894, ITER 895, ITER 896, ITER 897, ITER 898, ITER 899, ITER 900, ITER 901, ITER 902, ITER 903, ITER 904, ITER 905, ITER 906, ITER 907, ITER 908, ITER 909, ITER 910, ITER 911, ITER 912, ITER 913, ITER 914, ITER 915, ITER 916, ITER 917, ITER 918, ITER 919, ITER 920, ITER 921, ITER 922, ITER 923, ITER 924, ITER 925, ITER 926, ITER 927, ITER 928, ITER 929, ITER 930, ITER 931, ITER 932, ITER 933, ITER 934, ITER 935, ITER 936, ITER 937, ITER 938, ITER 939, ITER 940, ITER 941, ITER 942, ITER 943, ITER 944, ITER 945, ITER 946, ITER 947, ITER 948, ITER 949, ITER 950, ITER 951, ITER 952, ITER 953, ITER 954, ITER 955, ITER 956, ITER 957, ITER 958, ITER 959, ITER 960, ITER 961, ITER 962, ITER 963, ITER 964, ITER 965, ITER 966, ITER 967, ITER 968, ITER 969, ITER 970, ITER 971, ITER 972, ITER 973, ITER 974, ITER 975, ITER 976, ITER 977, ITER 978, ITER 979, ITER 980, ITER 981, ITER 982, ITER 983, ITER 984, ITER 985, ITER 986, ITER 987, ITER 988, ITER 989, ITER 990, ITER 991, ITER 992, ITER 993, ITER 994, ITER 995, ITER 996, ITER 997, ITER 998, ITER 999, ITER 1000, ITER 1001, ITER 1002, ITER 1003, ITER 1004, ITER 1005, ITER 1006, ITER 1007, ITER 1008, ITER 1009, ITER 1010, ITER 1011, ITER 1012, ITER 1013, ITER 1014, ITER 1015, ITER 1016, ITER 1017, ITER 1018, ITER 1019, ITER 1020, ITER 1021, ITER 1022, ITER 1023, ITER 1024, ITER 1025, ITER 1026, ITER 1027, ITER 1028, ITER 1029, ITER 1030, ITER 1031, ITER 1032, ITER 1033, ITER 1034, ITER 1035, ITER 1036, ITER 1037, ITER 1038, ITER 1039, ITER 1040, ITER 1041, ITER 1042, ITER 1043, ITER 1044, ITER 1045, ITER 1046, ITER 1047, ITER 1048, ITER 1049, ITER 1050, ITER 1051, ITER 1052, ITER 1053, ITER 1054, ITER 1055, ITER 1056, ITER 1057, ITER 1058, ITER 1059, ITER 1060, ITER 1061, ITER 1062, ITER 1063, ITER 1064, ITER 1065, ITER 1066, ITER 1067, ITER 1068, ITER 1069, ITER 1070, ITER 1071, ITER 1072, ITER 1073, ITER 1074, ITER 1075, ITER 1076, ITER 1077, ITER 1078, ITER 1079, ITER 1080, ITER 1081, ITER 1082, ITER 1083, ITER 1084, ITER 1085, ITER 1086, ITER 1087, ITER 1088, ITER 1089, ITER 1090, ITER 1091, ITER 1092, ITER 1093, ITER 1094, ITER 1095, ITER 1096, ITER 1097, ITER 1098, ITER 1099, ITER 1100, ITER 1101, ITER 1102, ITER 1103, ITER 1104, ITER 1105, ITER 1106, ITER 1107, ITER 1108, ITER 1109, ITER 1110, ITER 1111, ITER 1112, ITER 1113, ITER 1114, ITER 1115, ITER 1116, ITER 1117, ITER 1118, ITER 1119, ITER 1120, ITER 1121, ITER 1122, ITER 1123, ITER 1124, ITER 1125, ITER 1126, ITER 1127, ITER 1128, ITER 1129, ITER 1130, ITER 1131, ITER 1132, ITER 1133, ITER 1134, ITER 1135, ITER 1136, ITER 1137, ITER 1138, ITER 1139, ITER 1140, ITER 1141, ITER 1142, ITER 1143, ITER 1144, ITER 1145, ITER 1146, ITER 1147, ITER 1148, ITER 1149, ITER 1150, ITER 1151, ITER 1152, ITER 1153, ITER 1154, ITER 1155, ITER 1156, ITER 1157, ITER 1158, ITER 1159, ITER 1160, ITER 1161, ITER 1162, ITER 1163, ITER 1164, ITER 1165, ITER 1166, ITER 1167, ITER 1168, ITER 1169, ITER 1170, ITER 1171, ITER 1172, ITER 1173, ITER 1174, ITER 1175, ITER 1176, ITER 1177, ITER 1178, ITER 1179, ITER 1180, ITER 1181, ITER 1182, ITER 1183, ITER 1184, ITER 1185, ITER 1186, ITER 1187, ITER 1188, ITER 1189, ITER 1190, ITER 1191, ITER 1192, ITER 1193, ITER 1194, ITER 1195, ITER 1196, ITER 1197, ITER 1198, ITER 1199, ITER 1200, ITER 1201, ITER 1202, ITER 1203, ITER 1204, ITER 1205, ITER 1206, ITER 1207, ITER 1208, ITER 1209, ITER 1210, ITER 1211, ITER 1212, ITER 1213, ITER 1214, ITER 1215, ITER 1216, ITER 1217, ITER 1218, ITER 1219, ITER 1220, ITER 1221, ITER 1222, ITER 1223, ITER 1224, ITER 1225, ITER 1226, ITER 1227, ITER 1228, ITER 1229, ITER 1230, ITER 1231, ITER 1232, ITER 1233, ITER 1234, ITER 1235, ITER 1236, ITER 1237, ITER 1238, ITER 1239, ITER 1240, ITER 1241, ITER 1242, ITER 1243, ITER 1244, ITER 1245, ITER 1246, ITER 1247, ITER 1248, ITER 1249, ITER 1250, ITER 1251, ITER 1252, ITER 1253, ITER 1254, ITER 1255, ITER 1256, ITER 1257, ITER 1258, ITER 1259, ITER 1260, ITER 1261, ITER 1262, ITER 1263, ITER 1264, ITER 1265, ITER 1266, ITER 1267, ITER 1268, ITER 1269, ITER 1270, ITER 1271, ITER 1272, ITER 1273, ITER 1274, ITER 1275, ITER 1276, ITER 1277, ITER 1278, ITER 1279, ITER 1280, ITER 1281, ITER 1282, ITER 1283, ITER 1284, ITER 1285, ITER 1286, ITER 1287, ITER 1288, ITER 1289, ITER 1290, ITER 1291, ITER 1292, ITER 1293, ITER 1294, ITER 1295, ITER 1296, ITER 1297, ITER 1298, ITER 1299, ITER 1300, ITER 1301, ITER 1302, ITER 1303, ITER 1304, ITER 1305, ITER 1306, ITER 1307, ITER 1308, ITER 1309, ITER 1310, ITER 1311, ITER 1312, ITER 1313, ITER 1314, ITER 1315, ITER 1316, ITER 1317, ITER 1318, ITER 1319, ITER 1320, ITER 1321, ITER 1322, ITER 1323, ITER 1324, ITER 1325, ITER 1326, ITER 1327, ITER 1328, ITER 1329, ITER 1330,

# Success in skin allergy NGRA - NAMs aligned to skin sensitisation AOP



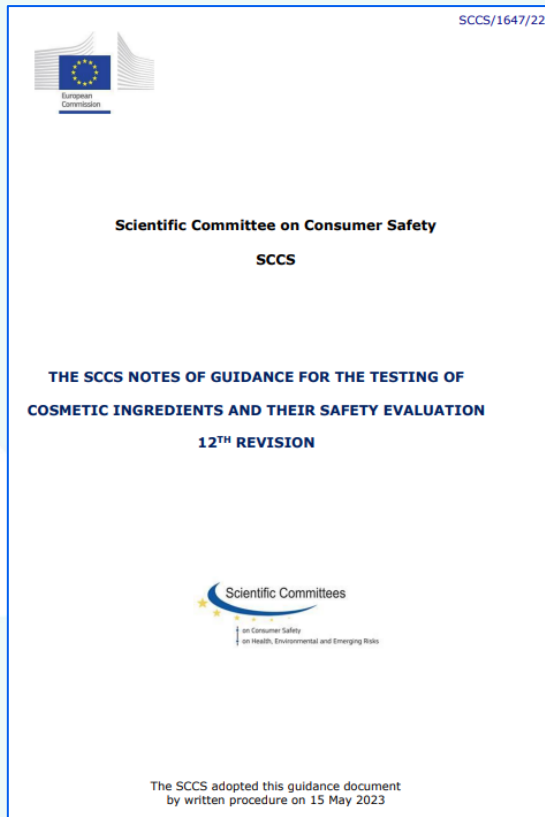
	Key Event 1 (KE1)	KE2	KE3	KE4	Adverse Outcome (AO)
<b>Predictive Chemistry</b> For example: • <a href="#">DEREK-NEXUS</a> • <a href="#">OECD QSAR Toolbox</a> • <a href="#">TIMES</a> • <a href="#">ToxTree</a>	<b>Protein Reactivity</b> <a href="#">OECD TG 442C</a> Includes: • ADRA • DPRA • kDPRA	<b>Keratinocyte Activation</b> <a href="#">OECD TG 442D</a> Includes: • KeratinoSens™ • LuSens	<b>DC Activation</b> <a href="#">OECD TG 442E</a> Includes: • h-CLAT • IL-8 Luc Assay • U-Sens™ • GARD™skin	<b>T Cell Proliferation</b> For Example: • Human T cell proliferation assays (hTCPA)	<b>Skin Sensitisation</b> <a href="#">OECD TG 429</a> : mouse local lymph node assay (LLNA) & variants <a href="#">TG442A</a> & <a href="#">442B</a> <a href="#">OECD TG 406</a> : Buehler & Guinea Pig Maximisation Test (GPMT)  Human evidence e.g. <a href="#">Human Repeat Insult Patch Test (HRIPT)</a>

  *in silico* NAM    
   *in chemico/vitro* NAM    
   *in vivo* evidence

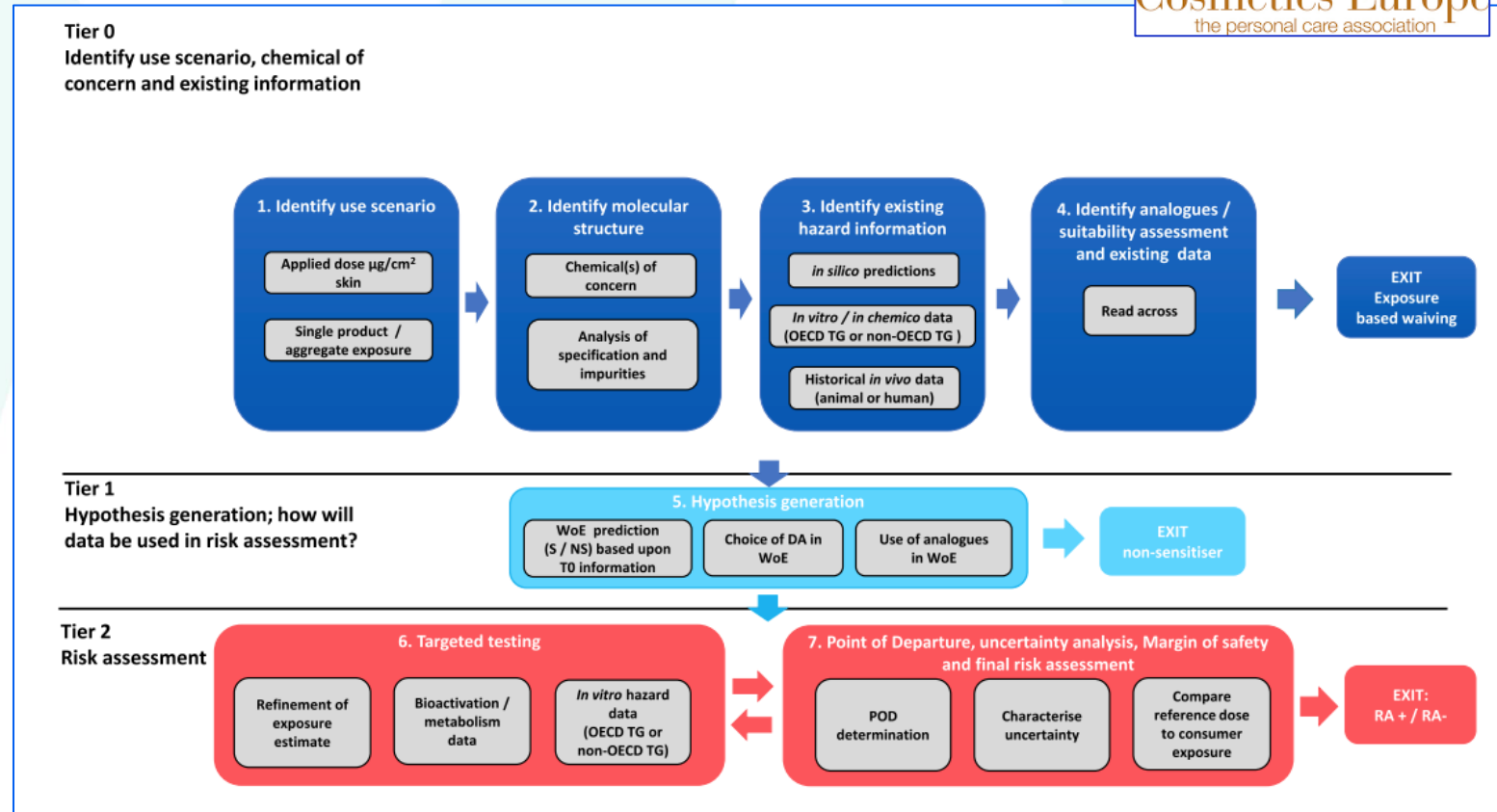


# Skin allergy risk assessment evolution

## SCCS 12<sup>th</sup> Notes of Guidance, 2023

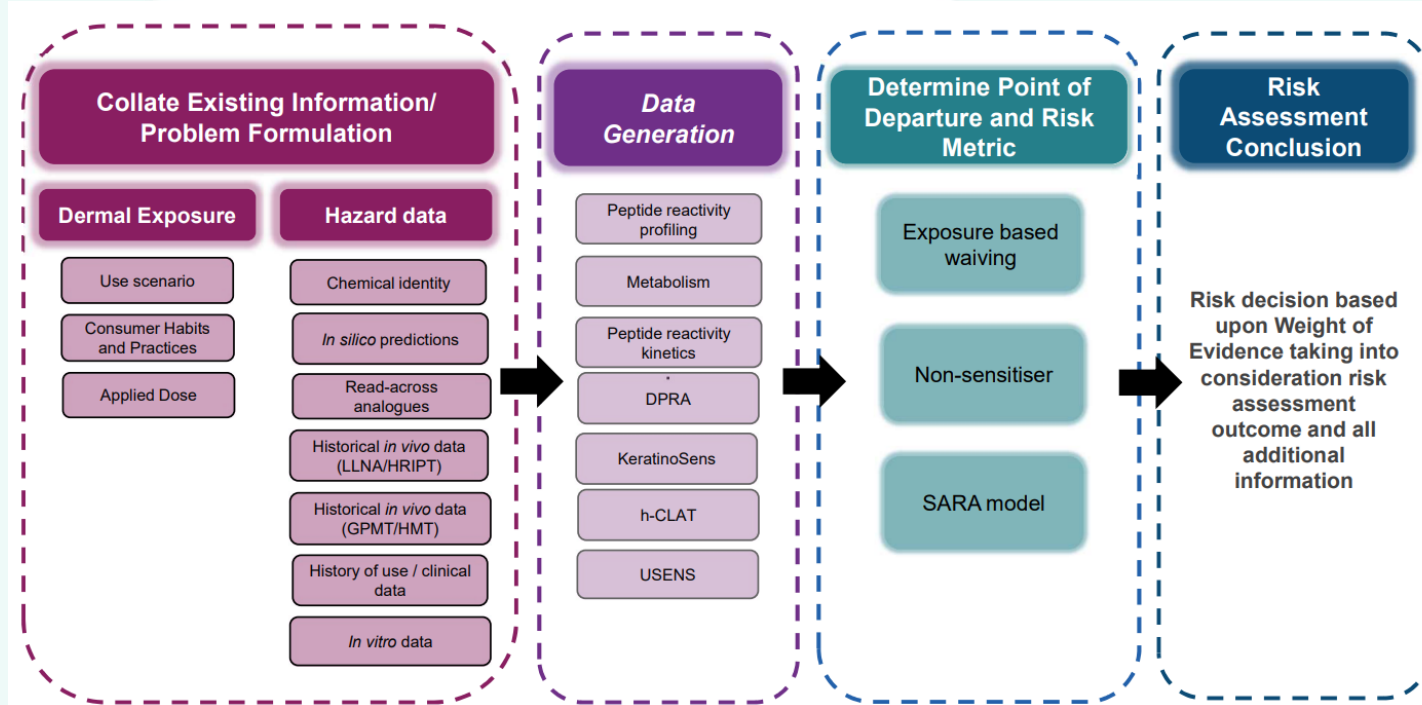


## Next generation risk assessment framework for skin sensitisation



Gilmour et al. Development of a next generation risk assessment framework for the evaluation of skin sensitisation of cosmetic ingredients. Regul. Toxicol. Pharmacol. 116, 2020.

# Next generation risk assessment (NGRA) framework for skin allergy



- Our NGRA framework for skin allergy is based upon the **International Cooperation on Cosmetics Regulation (ICCR) principles**<sup>1</sup> and the previously published **NGRA frameworks for systemic tox {Safety Evaluation Ultimately Replacing Animal Testing, SEURAT-1}**<sup>2</sup> and **skin allergy {Cosmetic Europe}**<sup>3</sup>.
- Designed to use a WoE based upon all available information, accommodates range of consumer product exposure scenarios and can provide a quantitative point of departure (PoD) and risk metric:  
→ **Skin Allergy Risk Assessment (SARA) Model**

<sup>1</sup>Dent et al. Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. *Comput. Toxicol.* 7, 20–26, 2018.

<sup>2</sup>Berggren et al. Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods. *Comput. Toxicol.* 4, 31–44, 2017.

<sup>3</sup>Gilmour et al.. Development of a next generation risk assessment framework for the evaluation of skin sensitisation of cosmetic ingredients. *Regul. Toxicol. Pharmacol.* 116, 2020.



# Introduction to the Skin allergy Risk Assessment (SARA) model



Unilever



# Skin Allergy Risk Assessment (SARA) model

## SARA Model Input Data Sources

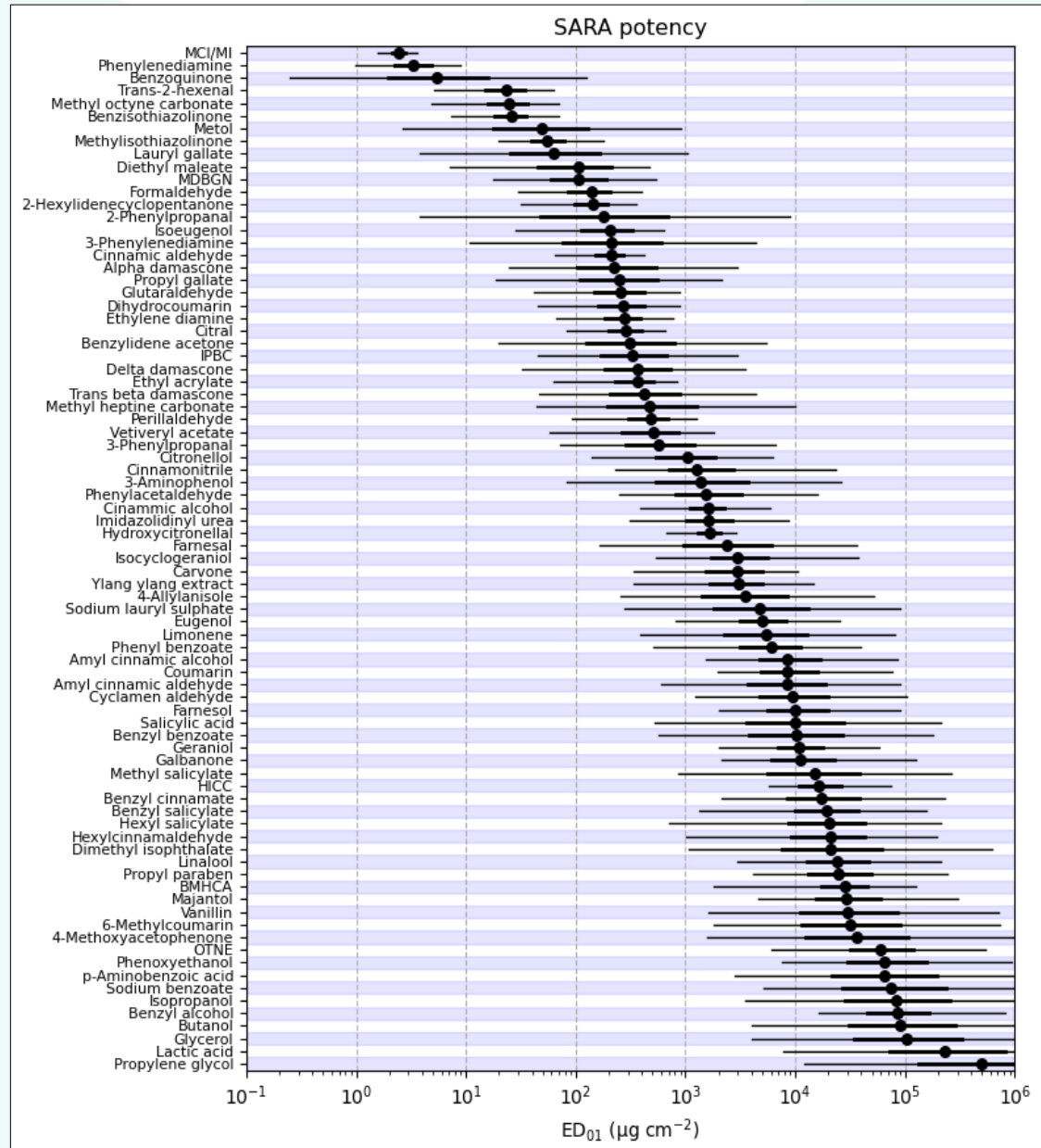
- ❖ Historical Local Lymph Node Assay (LLNA) data
- ❖ Historical Human Repeated Insult Patch Test (HRIPT) data
- ❖ *In vitro* data: DPRA (OECD TG442C), KeratinoSens™ (OECD TG 442D), h-CLAT (OECD TG 442E), U-SENS™ (OECD TG 442E)

## SARA Model Output Data Sources

- ❖ Point of Departure (PoD) termed the  $ED_{01}$  – the expected dose at which there is a 1% chance of skin sensitisation in a human (HRIPT) population
- ❖ Risk metric – p(low risk) of a given chemical exposure

- **Defined approach (DA) to provide potency and risk information based upon NAMs**
- **A Bayesian statistical approach** which can make potency and risk predictions using any combination of **historical *in vivo* (LLNA, HRIPT) or NAMs (DPRA, KeratinoSens™, h-CLAT and U-SENS™) – curated database of 81 chemicals**
- **Skin sensitiser potency is expressed as the  $ED_{01}$** , the dose estimated to induce sensitisation in 1% of a HRIPT population. This is the **Point of Departure (PoD)** for the risk assessment.
- **Risk metric:** SARA model also makes use of **benchmark exposures to infer a probability that a consumer exposure to a chemical is ‘low risk’**

# Potency across the SARA database - PoDs



This graph gives the ED<sub>01</sub> and quantified uncertainty (the dot with the 50% and 95% confidence intervals denoted by the thick and thin lines either side)

# Use of consumer exposure information and clinical evidence to develop skin allergy risk benchmarks

62 low or high risk benchmark exposures using 10 human skin allergens (e.g. MCI/MI) with an established history of use in 7 cosmetic product types.

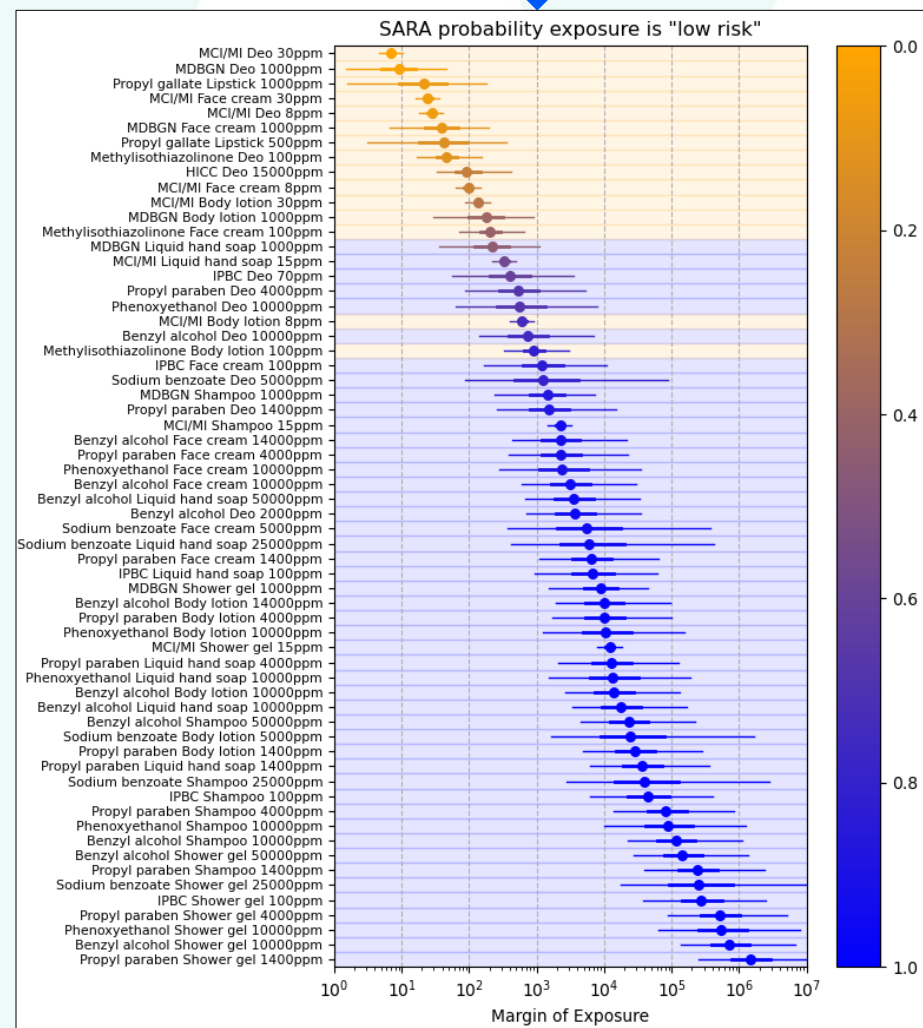
Margin of exposure (MoE) calculation (PoD/Exposure)

## Example

Material	Product type	Use level (ppm)	Consumer exposure to benchmark product (ng cm <sup>-2</sup> )	Induction risk
MCI/MI*	Deo	30	350	HIGH
		7.5	87.8	HIGH
	Face cream	30	100	HIGH
		7.5	25	HIGH
	Body lotion	30	18	HIGH
		7.5	4	HIGH
	Liquid hand soap	15	7.3	LOW
	Shampoo	15	1.1	LOW
Shower gel	15	0.2	LOW	

\*MCI/MI = Methylisothiazolinone/methylchloroisothiazolinone

- Probabilistic estimates of the MoE corresponding to each benchmark exposure at specific exposure level.
- Background colours indicate assigned risk category:
  - blue: low risk,
  - orange: high risk
- Shaded colours indicate the model-inferred risk. Ranking based on the median margin of exposure.



# **Skin Allergy Risk Assessment (SARA) Model Case Study**

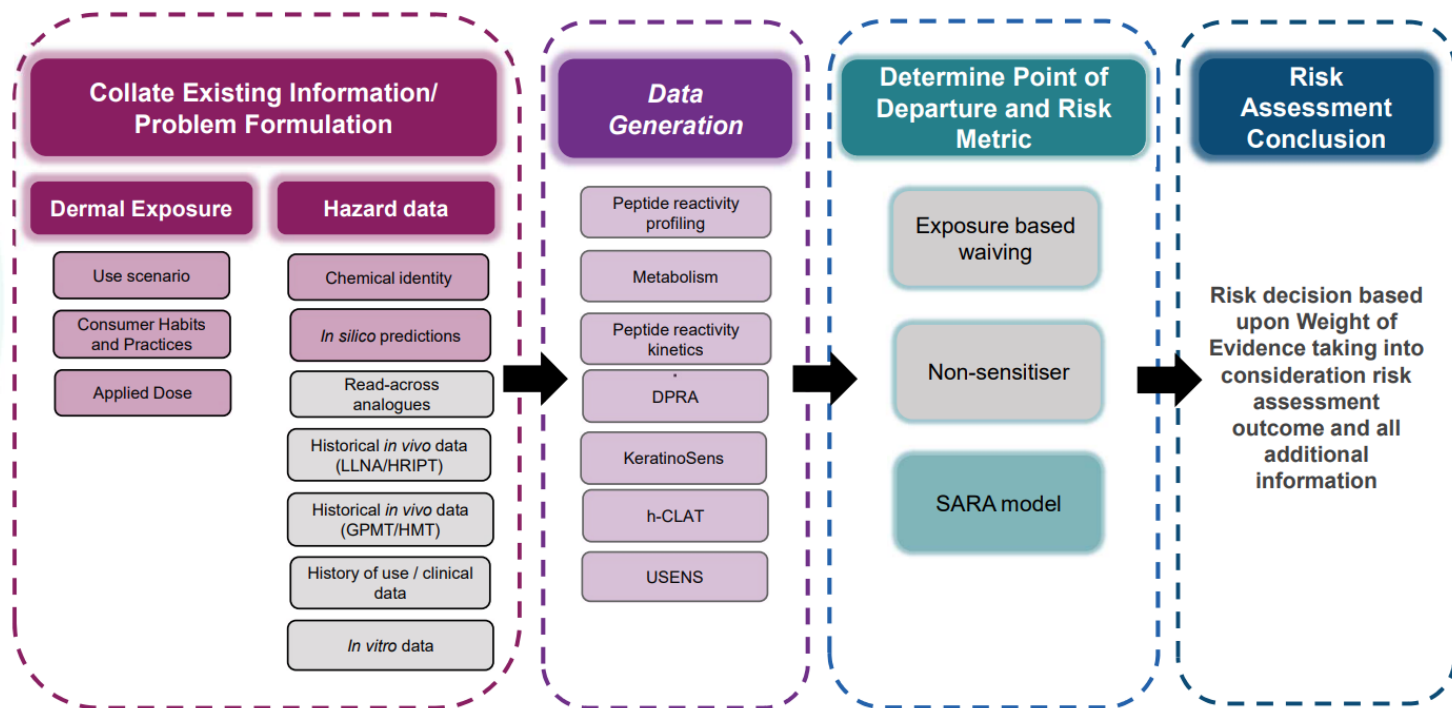
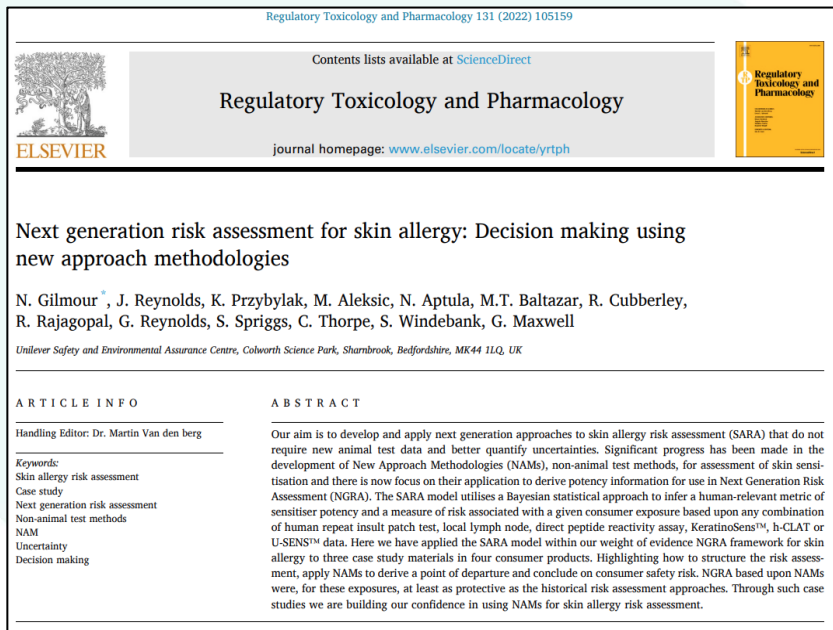
**0.02% (200ppm) geraniol in a face cream**



*Unilever*

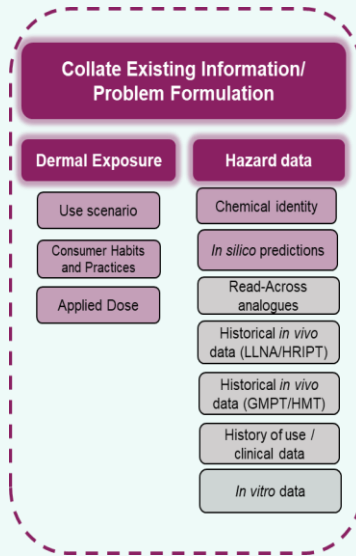


# Application of the NGRA framework for Skin Allergy



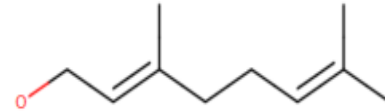
- Our NGRA framework is applied to a hypothetical skin allergy assessment of a consumer product:  
 → **0.02% (200ppm) geraniol in a face cream.**
- For the purposes of the case study, **historical *in vivo* data** and **read-across** were not used, and the use of **dermal sensitisation threshold** was not appropriate.

# Local exposure + Collate Existing Information/ Problem Formulation



## Geraniol

CAS 106-24-1



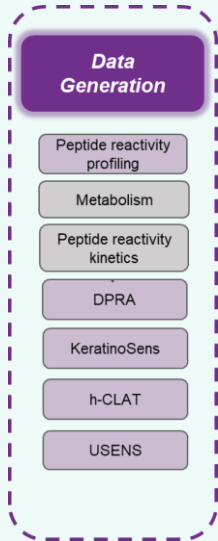
Product type	Face cream
Product used per day (90 <sup>th</sup> percentile) (g/day)	1.54
Ingredient inclusion level (%)	0.02
Skin surface area face (cm <sup>2</sup> )	565
Leave-on or Rinse-off	Leave-on
Local dermal exposure (µg/cm <sup>2</sup> )	0.544

\*Scientific Committee On Consumer Safety (SCCS), 2021. The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation. 11th Revision.

DEREK NEXUS	Alert – terpenoid EC3 model – 20% (weak)
TIMES-SS v.2.30.1.11 Skin Sensitisation model with autoxidation	Parent – Non sensitiser (in domain) Metabolites – Strong sensitiser- after autoxidation to disubstituted a,b-unsaturated aldehydes, Weak sensitiser after autoxidation to hydroperoxides
ToxTree v.3.1.0	Alert for Schiff base formation
OECD QSAR Toolbox v.4.4	<u>Protein binding by OECD</u> Parent - No alert found Skin Metabolites (2) - Direct Acting Schiff Base Formers >> Di-substituted alpha, beta-unsaturated aldehydes

- Geraniol is a reactive chemical and likely to be a skin sensitiser due to activation to a chemical capable of forming a Schiff base.
- Confidence in this prediction is high based upon chemical prediction consensus from all applied *in silico* tools.
- Data generation needs:
  - Assuming an abiotic activation mechanism (autoxidation), peptide reactivity profiling data should be generated to test this hypothesis. An estimation of potency is required to enable risk assessment for this exposure.
  - To enable a potency prediction using the SARA model DPRA, KeratinoSens<sup>TM</sup>, h-CLAT and U-SENS<sup>TM</sup> data should also be generated.

# Data Generation



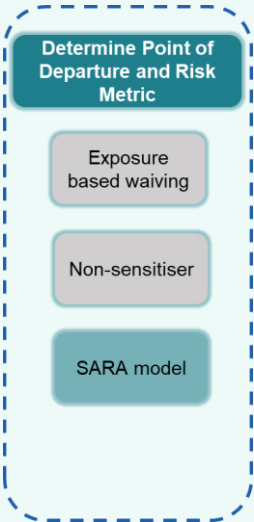
Reactivity Profiling (Aleksic et al., 2009 <sup>*</sup> )	DPRA (OECD TG442C <sup>**</sup> )	KeratinoSens <sup>TM</sup> (OECD TG 442D <sup>**</sup> )	h-CLAT (OECD TG 442E <sup>**</sup> )	U-SENS <sup>TM</sup> (OECD TG 442E <sup>**</sup> )
Cys (no adducts, 73.7%) Lys (no adducts, 3.5%) His (no adducts, -11.1%) <b>Arg (double Schiff base, 15.2%)</b> Tyr (no adducts, 8.2%) <b>N-term (acylation, Schiff base, 40.2%)</b> Ala (no adducts, -2.1%)	<b>Negative</b> Cys depletion 0% Lys depletion 10%	<b>Positive</b> EC <sub>1.5</sub> 110 µM EC <sub>3</sub> >2000 µM IC <sub>50</sub> 875 µM	<b>Positive</b> CD86 EC <sub>150</sub> 123 µg ml <sup>-1</sup> CD54 EC <sub>200</sub> - µg ml <sup>-1</sup> CV <sub>75</sub> 140 µg ml <sup>-1</sup>	<b>Positive</b> CD86 EC <sub>150</sub> 53.6 µg ml <sup>-1</sup> CV <sub>70</sub> 113.9 µg ml <sup>-1</sup>

- Geraniol was confirmed to be a **reactive chemical (Schiff base following autoxidation)** by peptide profiling where adducts consistent with formation of Schiff bases following oxidative activation were observed with the Arginine and N-terminus peptide.
- Geraniol demonstrated minimal depletion of Cys and Lys in the DPRA, which is consistent with the reactivity profiling data. Positive responses were evident in the KeratinoSens<sup>TM</sup>, h-CLAT and U-SENS<sup>TM</sup>.
- Thus, geraniol is a **skin sensitizer via Schiff base formation**.
- **Next step:** determination of the PoD, i.e. the human potency (ED<sub>01</sub>) → SARA model

<sup>\*</sup>Aleksic et al.. Reactivity profiling: covalent modification of single nucleophile peptides for skin sensitization risk assessment. Toxicol. Sci. 108, 401–411, 2009.

<sup>\*\*</sup>DPRA, KeratinoSens<sup>TM</sup>, h-CLAT and USENS<sup>TM</sup> data were sourced from the Cosmetics Europe database (Hoffmann et al. Non-animal methods to predict skin sensitization (I): the Cosmetics Europe database, Crit. Rev. Toxicol. 48, 344–358, 2018).

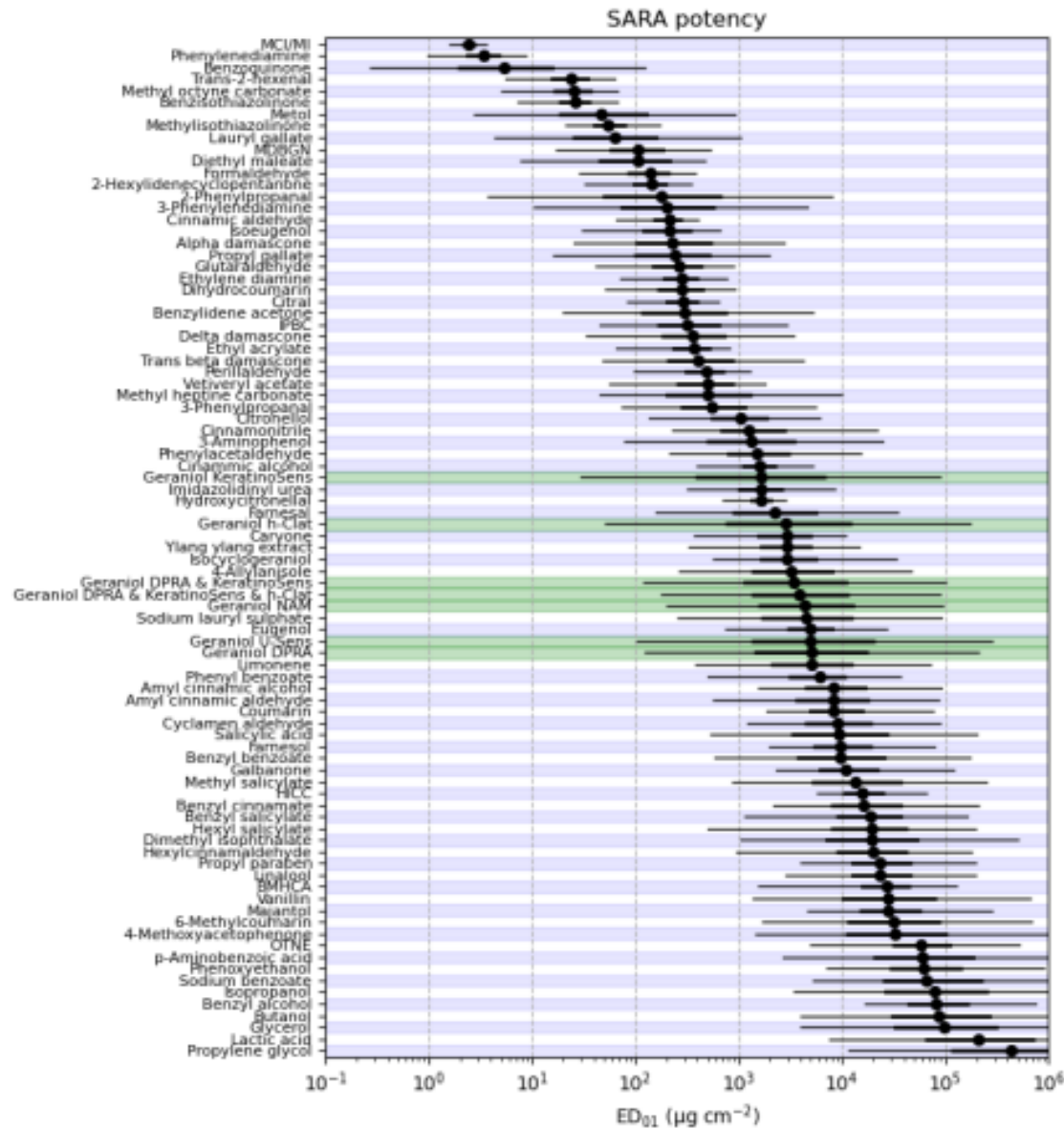
# Determine Point of departure using SARA DA



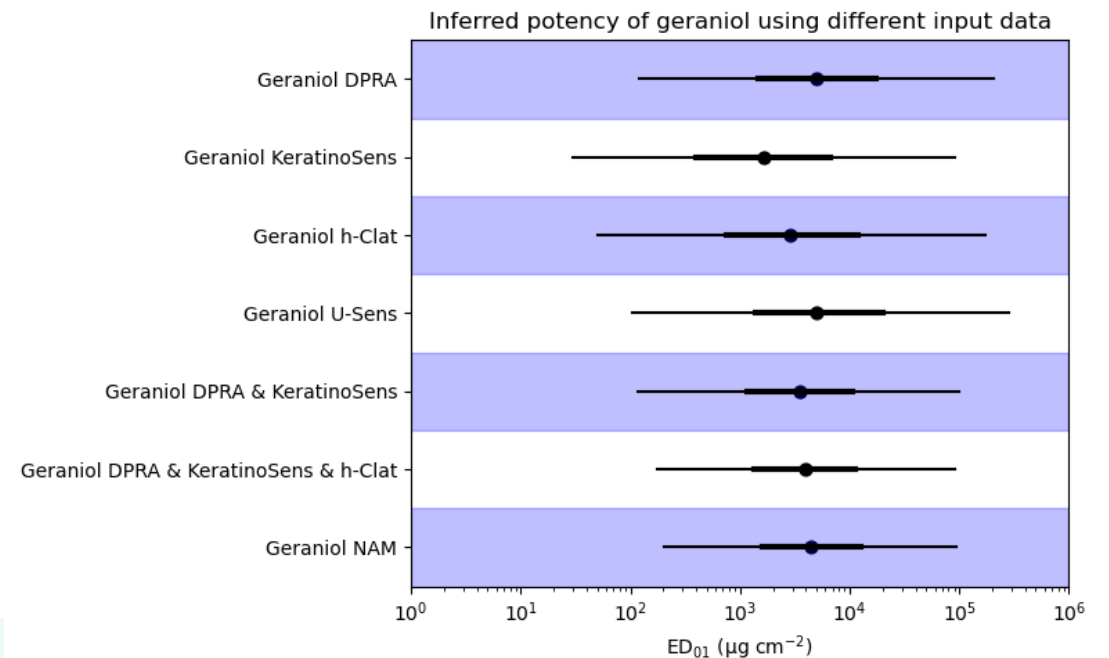
- The generated DPRA, KeratinoSens™, h-CLAT and U-SENS™ data were used as inputs into the SARA model to define a human relevant PoD (ED<sub>01</sub> i.e the 1% sensitising dose for a HRIPT population).
- For geraniol (NAM data only), the expected ED<sub>01</sub> is 4,500 µg cm<sup>-2</sup> (2.5<sup>th</sup> percentile: 180 µg cm<sup>-2</sup>, 97.5<sup>th</sup> percentile: 96,000 µg cm<sup>-2</sup>).
- Geraniol ranks with eugenol, which at least based upon LLNA data is reported to be of moderate potency



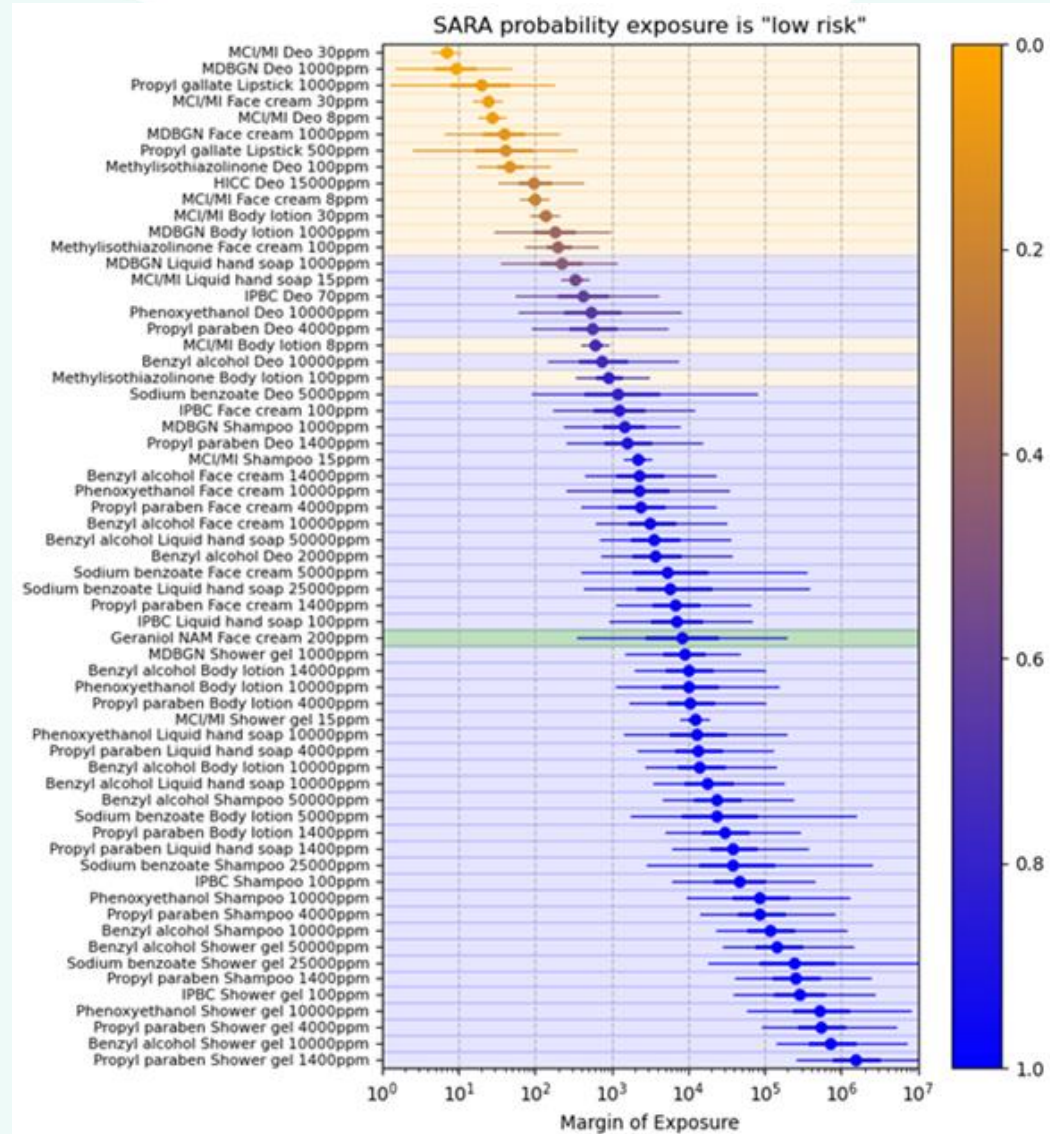
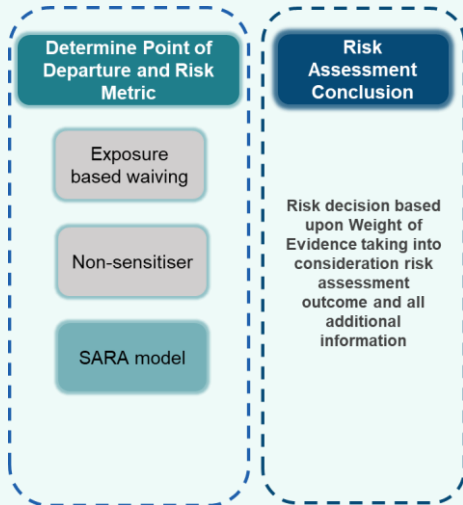
# SARA model: partial datasets



- The SARA model can make predictions based upon **any combination** of the DPRA, KeratinoSens™, h-CLAT and U-SENS™ data.
- Predictions made using just KeratinoSens™ or h-CLAT data yielded a marginally higher expected potency (lower ED<sub>01</sub>) compared with the predictions made using just DPRA or U-SENS™ data.
- Combining data increases the precision in the estimate of potency (reduced uncertainty).



# Determine MoE/Acceptable Exposure Level + NGRA conclusion



- The MoE was calculated from the ED<sub>01</sub> for geraniol and the dermal exposure for 0.02% geraniol in a face cream using SARA DA
- The MoE for 0.02% geraniol face cream exposure ranks with the low-risk benchmarks.
- The SARA DA probability that this exposure is low risk is calculated to be 0.95. Thus, there is a 95% probability that this exposure is low risk.
- Geraniol used at 0.02% (200 ppm) in a face cream is low risk for induction of skin sensitisation

# Conclusions & Next Steps

- Significant progress has been made in the last decade to apply non-animal experimental data using Defined Approaches (DAs) & tiered frameworks.
- Bayesian DAs enable experimental data variability to be modelled and uncertainty in PoDs & risk metrics to be factored into decision-making.
- Ongoing model development to expand the database, further incorporate mechanistic reactivity knowledge and explore new SARA inputs
- Recently published NGRA framework and case studies:
  - ✓ Cosmetic Europe NGRA framework (Gilmour et al., 2020)
  - ✓ Coumarin case study (Reynolds et al., 2021)
  - ✓ Unilever NGRA framework and other case studies (Gilmour et al., 2022; Gilmour et al., 2023)

Regulatory Toxicology and Pharmacology 116 (2020) 104721

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

Development of a next generation risk assessment framework for the evaluation of skin sensitisation of cosmetic ingredients

Nicola Gilmour<sup>a,1</sup>, Petra S. Kern<sup>b,1</sup>, Nathalie Alépée<sup>c</sup>, Fanny Boislève<sup>d</sup>, Dagmar Bury<sup>e</sup>, Elodie Clouet<sup>f</sup>, Morihiko Hirota<sup>g</sup>, Sebastian Hoffmann<sup>h</sup>, Jochen Kühnl<sup>i</sup>, Jon F. Lalko<sup>j</sup>, Karsten Mewes<sup>k</sup>, Masaaki Miyazawa<sup>l</sup>, Hayato Nishida<sup>m</sup>, Anne Osmant<sup>n</sup>, Dirk Petersohn<sup>o</sup>, Shuichi Sekine<sup>p</sup>, Erwin van Vliet<sup>q</sup>, Martina Klaric<sup>r</sup>

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

Next generation risk assessment for skin allergy: Decision making using new approach methodologies

N. Gilmour<sup>a</sup>, J. Reynolds, K. Przybylak, M. Aleksic, N. Aptula, M.T. Baltazar, R. Cubberley, R. Rajagopal, G. Reynolds, S. Spriggs, C. Thorpe, S. Windebank, G. Maxwell

Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, UK

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

A hypothetical skin sensitisation next generation risk assessment for coumarin in cosmetic products

G. Reynolds<sup>a</sup>, J. Reynolds, N. Gilmour, R. Cubberley, S. Spriggs, A. Aptula, K. Przybylak, S. Windebank, G. Maxwell, M.T. Baltazar<sup>a</sup>

Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, UK

Research Article

**Applying a Next Generation Risk Assessment Framework for Skin Sensitisation to Inconsistent New Approach Methodology Information**

Nicola Gilmour<sup>1</sup>, Nathalie Alépée<sup>2</sup>, Sebastian Hoffmann<sup>3</sup>, Petra S. Kern<sup>4</sup>, Erwin van Vliet<sup>5</sup>, Dagmar Bury<sup>6</sup>, Masaaki Miyazawa<sup>7</sup>, Hayato Nishida<sup>8</sup> and Cosmetics Europe<sup>9</sup>

<sup>1</sup>Unilever, Colworth Science Park, Bedford, United Kingdom; <sup>2</sup>L'Oréal, Research & Innovation, Aulnay-sous-Bois, France; <sup>3</sup>sch consulting + services, Paderborn, Germany; <sup>4</sup>Procter & Gamble Services NV/SA, Strombeek-Bever, Belgium; <sup>5</sup>Innovitox Consulting & Services, Houten, The Netherlands; <sup>6</sup>L'Oréal, Research & Innovation, Clichy, France; <sup>7</sup>Kao Corporation, Tochigi, Japan; <sup>8</sup>Shiseido Global Innovation Center, Kanagawa, Japan; <sup>9</sup>Brussels, Belgium

# NICEATM-Unilever CRADA



National Toxicology Program  
U.S. Department of Health and Human Services

## NICEATM News - 2021 Issue 25: May 27

### In this Newsletter:

#### **NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization**

#### **NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization**

NICEATM has entered into an agreement with consumer products company Unilever to collaboratively test and further develop their Skin Allergy Risk Assessment (SARA) predictive model. SARA is a computational model that uses a variety of input data to estimate a probability that a chemical will cause an allergic skin reaction in humans. NICEATM will test the SARA model using a variety of chemical data sets, including chemicals of interest to U.S. and international regulatory agencies. NICEATM and Unilever will also work together to expand the SARA model to include data generated by NICEATM. The intent is to make the SARA model openly available for public use along with other NICEATM predictive models. Availability of the SARA model will help further reduce animal use for the endpoint of skin sensitization, and will improve upon existing efforts by providing points of departure for quantitative human risk assessment.

[Information about other NICEATM projects](#) to evaluate alternatives to animal use for skin sensitization is available at <https://ntp.niehs.nih.gov/qo/ACDtest>.

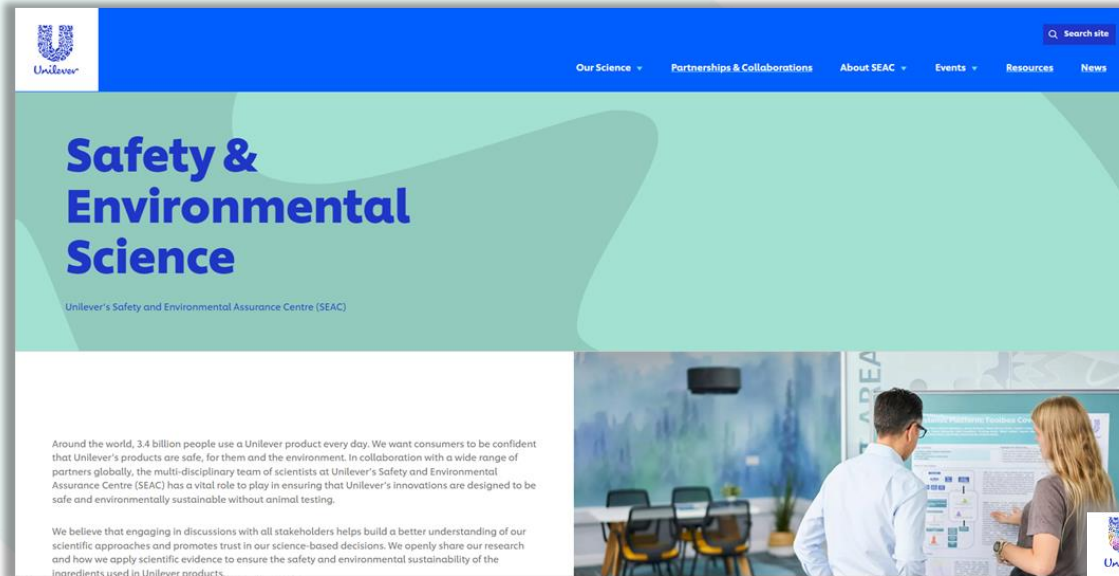
Reference: [Reynolds et al.](#) Probabilistic prediction of human skin sensitizer potency for use in next generation risk assessment. *Comput Toxicol* 9:36-49. <https://doi.org/10.1016/j.comtox.2018.10.004>

- Unilever-NICEATM CRADA underway to develop a publicly available version of the SARA Model for evaluation as part of the OECD workplan for OECD DASS TG 497



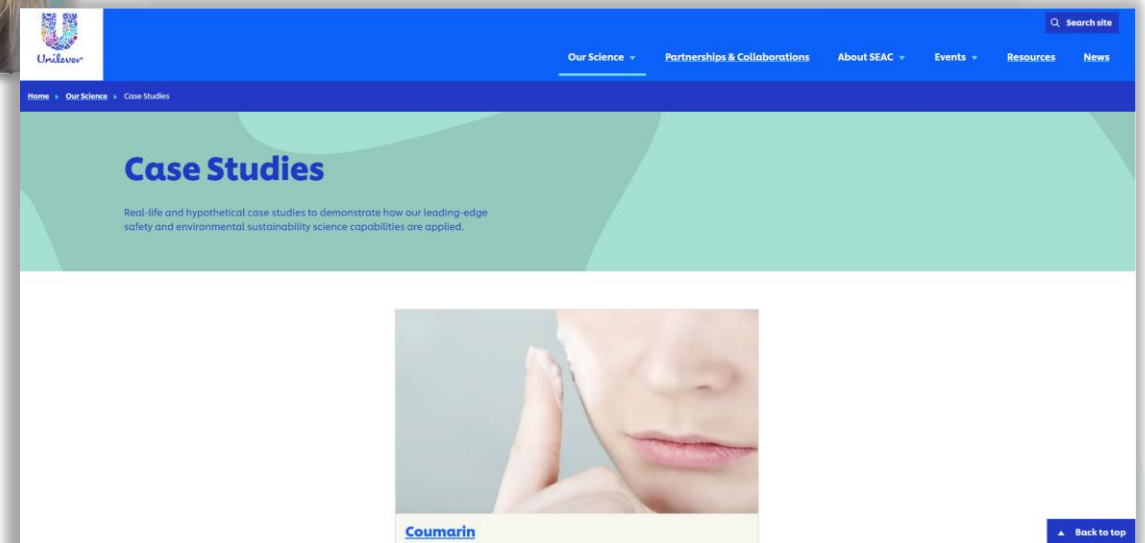
# Safety & Environmental Sciences website:

<https://seac.unilever.com/>



- **Summary of SEAC science capabilities for expert audiences:** industry, regulator & academic scientists

- **Microsite covering:**
  - Our Science → **case studies**
  - Partnerships & Collaborations
  - About SEAC
  - Events
  - Resources
  - News



<https://seac.unilever.com/our-science/case-studies/coumarin/>

# Série de Webinars em Ciência *In Vitro*



<https://seac.unilever.com/news/2022/seac-scientists-collaborate-to-launch-latam-in-vitro-science-webinars/>

## Tópicos já abordados:

## Em português e/ou espanhol!

- Sensibilização dérmica
- Irritação ocular e dérmica
- Segurança ambiental
- Processo de validação de métodos alternativos
- Status regulatório no Brasil e América Latina
- Química analítica na avaliação de segurança humana e ambiental

Gravação dos Eventos passados podem ser acessados:



<https://www.youtube.com/@laboratoriotoxin5356/playlists>

# Master Class in Animal-Free Safety Assessment for Cosmetics

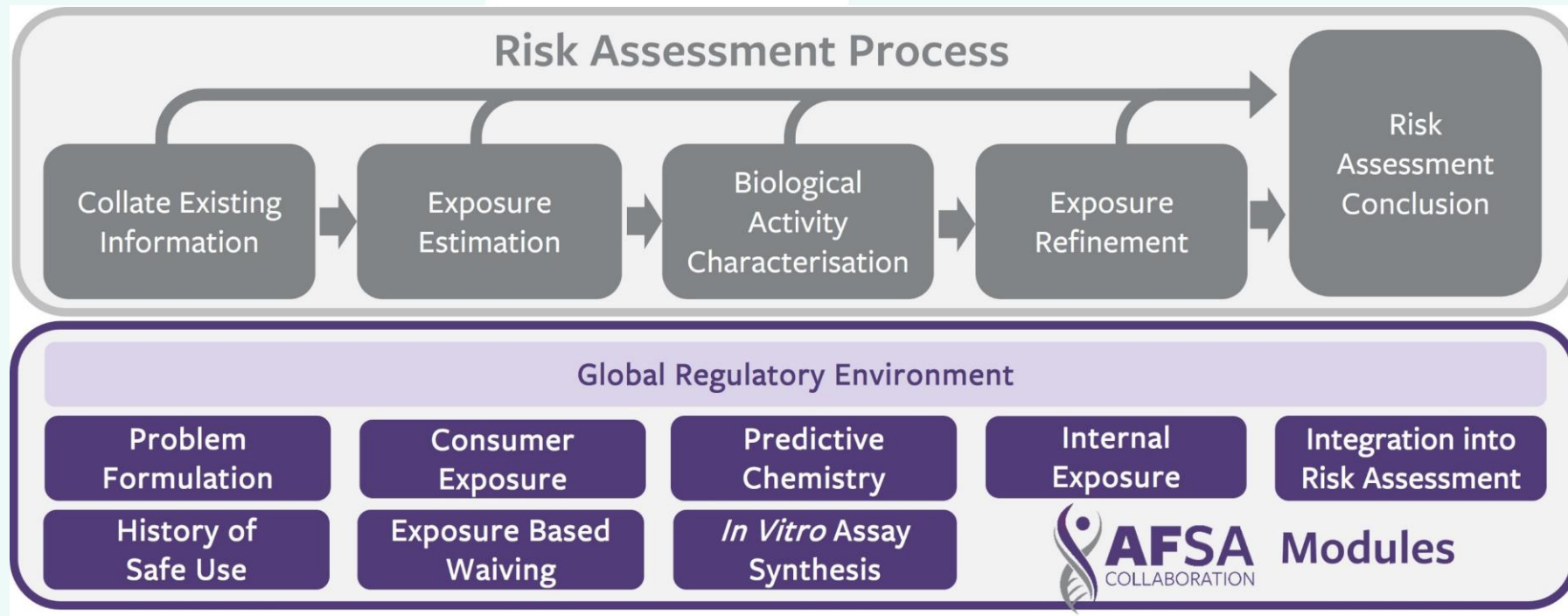
- Covering Risk Assessment from start to finish

## Audience:

- Product and chemical safety assessors and regulators
- Regulatory affairs and compliance specialists
- CRO/GLP laboratories
- Small and medium enterprises
- Graduate students
- Non-governmental organizations



<https://www.afsacollaboration.org/masterclass/>





# Acknowledgements

Georgia Reynolds

Nicola Gilmour

Joe Reynolds

Maja Aleksic

Nora Aptula

Gavin Maxwell

Ramya Rajagopal

Sandrine Spriggs

Charlotte Thorpe

Sam Windebank

Katarzyna Przybylak

Maria Baltazar

Paul Russell

Richard Cubberley

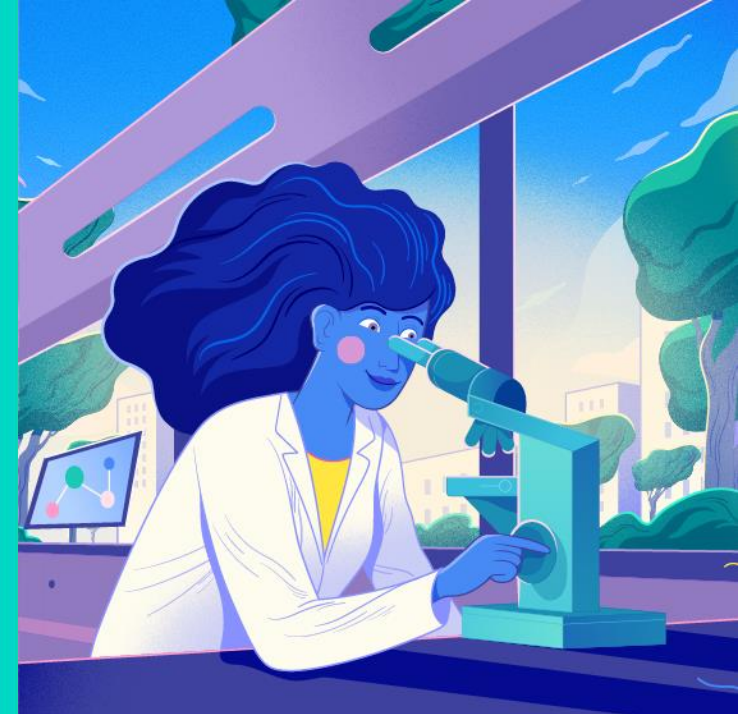
Matt Dent

Carl Westmoreland

Julia Fentem



Associação Brasileira da Indústria de  
Higiene Pessoal, Perfumaria e Cosméticos



Unilever