Data Supplement

Publications

2-Bromo-2-Nitropropane-1,3-Diol

Alkyl Gallates

Phosphine Oxides & Phosphinates

Phthalates

Polyacrylate-13

Prostaglandin Analogs

Pyrogallol

EXPERT PANEL MEETING

OCTOBER 5-6, 2026

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Bart Heldreth, PhD, Executive Director, CIR
Date: September 25, 2026
Subject: Wave 2 – FYI Publications

Please find attached the two recent publications, purely for your information. (*Zhu - Fifty Years of CIR and the Expert Panel* and *Klaassen - Words matter in toxicology and risk assessment*). Please note, no action is being requested thereon.

Check for updates

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Fifty Years of the Cosmetic Ingredient Review (CIR) and the Expert Panel for Cosmetic Ingredient Safety: An Independent, Transparent, and Science-Forward Program for Ingredient Safety Assessment

Jinqiu Zhu[1], Wilma F. Bergfeld[2], Monice Fiume[3], and Bart Heldreth[4]

Abstract

The Cosmetic Ingredient Review (CIR) program marks its 50th anniversary as an enduring model of independent, transparent, and science-forward evaluation of cosmetic ingredient safety. Established in 1976 by the Personal Care Products Council (PCPC), with the support of the US Food and Drug Administration (FDA) and the Consumer Federation of America (CFA), CIR has completed evidence-based safety assessments for more than 6000 ingredients, with comprehensive findings published in *International Journal of Toxicology*. Through a defined governance framework, Expert Panel review, and fully public deliberations, CIR conducts safety evaluations via a structured and transparent process that incorporates broad stakeholder engagement. The program has continued to evolve in parallel with global regulatory and methodological advances. CIR remains an independent scientific resource that complements regulatory oversight and supports robust safety substantiation of cosmetic products. In addition, it has increasingly adopted an exposure-driven evaluation paradigm aligned with Next-Generation Risk Assessment (NGRA) principles, integrating validated New Approach Methodologies (NAMs) to inform hazard identification and refine risk characterization while complementing traditional toxicology. Collectively, these efforts promote scientific harmonization and the continued modernization of cosmetic ingredient safety assessment. At 50 years, CIR stands as a globally recognized, science-based, and publicly accountable program, exemplifying independence and advancing integrated, exposure-led, and human-relevant risk assessment consistent with modern regulatory science.

Keywords

CIR, cosmetic ingredient safety, Expert Panel, MoCRA, NGRA, NAM, WoE

Introduction: Fifty Years of Scientific Oversight in Cosmetic Ingredient Safety

The Cosmetic Ingredient Review (CIR) program marks its 50th anniversary as a globally recognized model for independent, transparent, and science-based evaluation of cosmetic ingredient safety. Established in 1976 by the Cosmetic, Toiletry, and Fragrance Association (CTFA, now the Personal Care Products Council (PCPC)) in cooperation with the US Food and Drug Administration (FDA) and the Consumer Federation of America (CFA), CIR was founded as a not-for-profit program to fill a critical gap in publicly available cosmetic safety substantiation.[1,2] No legislation mandates the premarket approval of cosmetic products; manufacturers remain responsible for ensuring the safety of ingredients used in finished products.[3] The safety assessments of CIR and the Expert Panel for Cosmetic Ingredient Safety (Expert Panel), however, are a freely available resource that manufacturers can use to meet their burden of safety substantiation. These same assessments have also become a critical decision-making resource for toxicologists and dermatologists around the world and across industries.

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Since its inception, CIR has provided evidence-based safety assessments of cosmetic ingredients through an open and collaborative process that engages representatives from government, consumer groups, industry, and the public. Over the past five decades, CIR has systematically evaluated more than 6000 cosmetic ingredients. While CIR does not conduct or fund new laboratory research, it synthesizes the existing evidence to establish conditions of safe use, providing a robust, independent, scientific resource for scientists, clinicians, regulators, and industry. Expert Panel deliberations prompt data submission from stakeholders, along with recommended actions for further investigation and risk mitigation.

The Modernization of Cosmetics Regulation Act of 2022 (MoCRA) strengthened national oversight of cosmetic safety and reinforced the importance of robust, well-documented, and science-based safety substantiation.[4,5] Under MoCRA, the responsible person—i.e., the manufacturer, packer, or distributor of a cosmetic product whose name appears on the product label, and who bears legal responsibility for compliance—is required to ensure and maintain records demonstrating adequate substantiation of cosmetic product safety. Within this evolving regulatory landscape, CIR continues to serve as an independent scientific resource, advancing consumer protection through evidence-based evaluations that define the conditions of safe use for cosmetic ingredients. In recent years, CIR has modernized its scientific framework in alignment with global regulatory and methodological advances, drawing on principles established by the Organisation for Economic Co-operation and Development (OECD), the International Cooperation on Cosmetics Regulation (ICCR), and the International Collaboration on Cosmetics Safety (ICCS), as well as scientific guidance and risk-assessment practices articulated by the EU Scientific Committee on Consumer Safety (SCCS). To enhance the robustness and human-health relevance of safety evaluations, CIR has adopted exposure-driven risk assessment paradigms. In parallel, it has progressively integrated New Approach Methodologies (NAMs) within the Next-Generation Risk Assessment (NGRA) framework to complement traditional toxicological data, supported by predictive in silico analyses, mechanistic in vitro evidence, adverse outcome pathway (AOP)-informed evaluation and physiologically based kinetic/pharmacokinetic (PBK/PBPK) modeling. CIR has also formalized its read-across practices—through initiatives such as the Read-Across Working Group (RAWG)—to promote structured group evaluations, transparent documentation of uncertainty, and the robustness of the Weight of Evidence (WoE). Collectively, these advancements have strengthened the scientific consistency, efficiency, and human-relevance of CIR's ingredient safety evaluations, while also supporting the reduction of animal testing in line with evolving regulatory and ethical expectations.

At 50 years, the CIR program exemplifies a mature, evidence-based, and publicly accountable model of cosmetic ingredient safety evaluation. It continues to evolve in step with methodological and strategic advances, regulatory changes introduced by MoCRA, and emerging public-health priorities. In doing so, CIR is advancing toward an integrated, exposure-informed, human-relevant risk assessment paradigm that aligns with contemporary regulatory science, while maintaining its core commitments to independence, transparency, and scientific rigor.

This article provides an updated overview of the CIR program, outlining its review process, key achievements, current challenges, and ongoing initiatives that shape its continued evolution and future directions.

Governance Structure and Operation of the CIR Program

The CIR program is guided by the Cosmetic Ingredient Review Procedures & Support to the Expert Panel for Cosmetic Ingredient Safety.[2] These Procedures establish the framework for CIR operations, defining the roles of the Steering Committee, the Expert Panel, the CIR staff, and the CIR Science and Support Committee (CIR SSC), as well as the process for prioritizing the review of ingredients as used in personal care products.

As illustrated in Box 1, the CIR Steering Committee, consisting of three industry representatives and four public representatives, provides overall policy direction and program oversight, and elects members of the Expert Panel, including the Chair. The CIR Executive Director is appointed by the Chair of the Steering Committee, subject to approval by the Chairs of the PCPC Board of Directors and the PCPC Scientific Advisory Committee Executive Committee. While the Steering Committee has no role in the Expert Panel's scientific deliberations or safety conclusions, it may propose revisions to the CIR Procedures.

Box 1. Composition and Representation of CIR Steering Committee

Three Industry Representatives:

The president and CEO of the PCPC – Chair of the Steering Committee
Chair of PCPC's CIR SSC
PCPC executive vice president for science

Four Public Representatives:

The Wilma Fowler Bergfeld Chair of the *Expert Panel*
A dermatologist nominated by the *American Academy of Dermatology* (AAD)
A consumer representative nominated by the *Consumer Federation of America* (CFA)
A toxicologist nominated by the *Society of Toxicology* (SOT)

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The Expert Panel serves as the independent scientific decision-making body of the CIR program. The voting Expert Panel members are appointed through a public nomination process, with candidates typically recommended by the Society of Toxicology (SOT) and the American Academy of Dermatology (AAD), although nominations from any qualified individual or organization are accepted. Panelists are selected for their expertise, which is necessary for the assessment of cosmetic ingredient safety, and must have no financial conflicts of interest with the personal care products industry. They are subject to the conflict-of-interest requirements as stated on the Expert Panel's website (https://ingredientsafetyexpertpanel.org/conflict-of-interest-statement/).

The Expert Panel comprises nine voting members with expertise across dermatology, chemistry, toxicology, pharmacology, pathology, and veterinary medicine, including physicians, professors, department heads, and leaders of scientific and professional associations. The current membership of the Expert Panel is available on their website (https://ingredientsafetyexpertpanel.org/membership/). In addition, the Expert Panel includes three non-voting liaison members representing the US FDA, the CFA, and the PCPC. These liaisons participate fully in all deliberations to facilitate communication among government, consumer groups, and industry stakeholders, but do not vote on safety conclusions.

The Panel operates in two teams, each led by a distinguished dermatologist and including at least one toxicologist and one chemist to ensure balanced scientific evaluation. Dr Wilma Bergfeld, the current Wilma Fowler Bergfeld Chair (named after her this year) of the Expert Panel, has served the CIR program in multiple leadership roles since its inception and has chaired the Expert Panel since 1991. When required, the Chair serves as the tiebreaking vote. Dr Bergfeld has held numerous leadership positions in academic/clinical medicine and professional societies, including serving as President of the American Academy of Dermatology and the Women's Dermatologic Society, and as Head and Co-Director of Dermatopathology at the Cleveland Clinic. She has also served on several US FDA advisory committees.

The CIR staff provides scientific and administrative support to the Expert Panel in the assessment of cosmetic ingredient safety. The team consists of 9 people and is led by the Executive Director, Dr Bart Heldreth, who holds overall authority and responsibility for the daily management of the CIR staff and coordination of Expert Panel activities. Current information on the CIR staff is available on the CIR website (https://www.cir-safety.org/about).

Industry participation in the CIR program is in a transparent manner through the voluntary submission of unpublished safety data from their own testing. In addition, the PCPC convenes the CIR SSC, comprising industry scientists who facilitate the public exchange of technical information with the CIR staff and Expert Panel during the preparation of safety assessments. Under the CIR Procedures, the CIR SSC is prohibited from providing policy guidance or direction to either the staff or the Expert Panel. At the request of the Expert Panel, however, the SSC may be tasked with compiling data or conducting analyses to address data gaps or specific scientific questions. Through this open and publicly documented process, the CIR SSC contributes specialized expertise that supports comprehensive, evidence-based, and well-informed safety evaluations by the Expert Panel.

CIR's Role in the Post-MoCRA Era: Scientific Independence, Transparency, and Public Engagement

The enactment of MoCRA has enhanced the US regulatory framework for cosmetic safety by requiring that each product be supported by adequate scientific evidence demonstrating safety under its intended conditions of use.[4] While operating outside MoCRA's enforcement structure as an independent, non-regulatory scientific forum, CIR plays a complementary, science-based role by delivering transparent, evidence-based safety assessments informed by collaboration among multiple stakeholders. These evaluations help define the conditions of safe use and provide decision-relevant scientific foundations that responsible persons may apply to substantiate product safety and manage risk in alignment with MoCRA requirements. In doing so, CIR supports regulatory compliance while promoting consumer protection. The US FDA provides guidance on how manufacturers can use safety data that is already available on individual ingredients, including CIR as one such resource (https://www.fda.gov/cosmetics/cosmetics-science-research/product-testing-cosmetics).

Governance: Ensuring Independence and Scientific Integrity

CIR maintains independence and scientific integrity through a tripartite governance structure that separates program administration from scientific judgment. The Expert Panel makes all scientific decisions free from financial conflicts-of-interest; the PCPC provides funding and technical support without influencing those decisions; and the US FDA and CFA attend as non-voting observers, contributing regulatory and consumer perspectives while preserving the Panel's independence. This balanced structure sustains CIR's credibility in the post-MoCRA era, where impartial, evidence-based safety substantiation is essential.

Operational Transparency and Public Engagement: A Model of Open Scientific Review

CIR maintains transparency and actively engages the public and stakeholders throughout its safety assessment process. From initial ingredient selection to issuance of the final report, the process remains open to review and critique by all interested parties, ensuring a continuous cycle of feedback and improvement.

Expert Panel meetings, whether held in-person or virtually, are open to the public and include designated time for stakeholder comments. Draft versions of ingredient safety dossiers are posted online approximately 3 weeks prior to each meeting. Each safety assessment is discussed and voted on during a public session before being released for a 60-day public comment period. All comments received are documented, addressed in follow-up discussions, and reflected in the public docket. CIR does not accept confidential or proprietary information; all data reviewed by the Panel are accessible on the CIR website or available upon request. The status of ongoing reviews can be tracked at https://www.cir-safety.org, and inquiries or submissions may be directed to cirinfo@cir-safety.org. Through this open, iterative, and evidence-based framework, CIR promotes public accountability and maintains the scientific robustness and independence of its safety assessments.

The CIR Safety Assessment Process

The CIR safety assessment process is a structured, transparent, and science-driven procedure that governs the evaluation of cosmetic ingredients from initial prioritization to peer-reviewed publication of final safety determinations. It begins with annual ingredient prioritization based on exposure frequency, emerging scientific concerns, and data availability. Each selected ingredient then undergoes a multi-phase review following a defined structure: scientific literature review (SLR) → draft report (DR) → (insufficient data announcement (IDA), if needed) → tentative report (TR) → final report (FR) → peer-reviewed publication, with each stage and decision documented and publicly traceable. Public and stakeholder input is actively solicited through posted drafts and open Expert Panel discussions. In addition, a periodic re-review mechanism ensures that CIR conclusions remain current with changing ingredient use patterns and advances in scientific understanding.

Ingredient Selection, Grouping, and Read-Across Strategies

Ingredient Selection and Prioritization. Each year, the Expert Panel and CIR staff select a priority list of ingredients to be assessed for safety in the upcoming year. The selection process begins with consideration of substances reported to be in current use in the US cosmetics market and listed in the *International Cosmetic Ingredient Dictionary* (*Dictionary*), which now includes more than 35 000 individual ingredients that have been, are currently, or are potentially intended for cosmetic use.[6]

Under the CIR Procedures, certain ingredients may be excluded from CIR review when their safety is already being evaluated by another recognized authority.[2] For instance, fragrance ingredients under review by the Research Institute for Fragrance Materials (RIFM) are generally excluded when their only reported function in cosmetics is as a fragrance. Likewise, ingredients currently being reviewed by the US FDA as over-the-counter (OTC) drug actives, food flavorings, or food substances generally recognized as safe (GRAS) may be deferred from CIR consideration until the FDA's evaluation is complete.

The CIR therefore focuses its assessments on ingredients reported as being used in cosmetics marketed in the US. Historically, this information was obtained through the FDA's Voluntary Cosmetic Registration Program (VCRP),[7] which collected data submitted voluntarily by industry on cosmetic ingredients and the product categories in which they were used. Post-MoCRA, FDA has replaced the VCRP with a mandatory system—the Registration and Listing Database (RLD) of cosmetic products, which requires facilities that manufacture or process cosmetics for US distribution to register with the FDA, and responsible persons therein to submit product listings that include facility identifiers, brand names, product categories, and complete ingredient lists.[4,8] Some small businesses are exempt, except when manufacturing eye area products, injected products, internal use products, or products that alter appearance for more than 24 hours. This new framework enhances transparency, traceability, and regulatory oversight of cosmetic products and their ingredients. However, small-businesses exemptions may result in incomplete representation of cosmetic products within the RLD, thereby limiting the comprehensiveness of ingredient use data across the US market. As of July 2025, the RLD dataset included 784 270 unique product records across 17 major product categories and approximately 91 subcategories,[8] spanning a wide range of cosmetic types, such as baby care, hair care, skin care, makeup, and fragrance, and encompassing both leave-on and rinse-off formulations, including liquids and sprays applied by traditional or airbrush methods.

When developing the annual CIR Priority List, several key considerations guide ingredient selection. The Panel and staff first evaluate the frequency of use, reflected by the number of reported product formulations containing a given ingredient, as an indicator of potential consumer exposure. In addition to usage data, the Panel considers whether there are specific indicators of potential safety risk, such as newly identified toxicological findings, adverse event reports, or emerging regulatory concerns. Ingredients that have attracted regulatory attention, generated adverse event reports, or been associated with new toxicological findings may be prioritized for new evaluation or re-review (if the Expert Panel has previously assessed the safety thereon).

These risk-informed considerations are complemented by a transparent nomination process that invites stakeholder input. Any ingredient may be nominated for inclusion by government agencies, industry representatives, non-governmental organizations, members of the general public, or even the Expert Panel and CIR staff, regardless of whether it has been previously reviewed. Ingredients may also come to the Expert Panel's attention through nomination "for cause" (e.g., identification by the FDA as an ingredient of concern) or through emerging scientific reports suggesting potential health risks. Illustrative examples include industry-nominated ingredients such as 1,2,4-Trihydroxybenzene; substances requested by the US FDA (e.g., Toluene and *tert*-Butylhydroquinone); ingredients nominated by an Expert Panel member (e.g., *p*-Phenylenediamine); and

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designation by the American Contact Dermatitis Society (ACDS) as the "Allergen of the Year" (e.g., Toluene-2,5-Diamine Sulfate).

CIR also includes at least one representative hair dye ingredient on each annual Priority List to ensure that these ingredients, which typically have low frequencies of use, are evaluated on an ongoing basis within the CIR safety assessment program. For example, Basic Orange 3 was nominated by the industry-formed Hair Color Technical Committee (HCTC) as the 2026 annual hair ingredient and it was added to the Priority List of that same year.

In addition, the Panel systematically schedules re-reviews of ingredients for which previous safety assessments were completed more than 15 years earlier. Updated literature searches are conducted to determine whether new data, expanded cosmetic applications (e.g., newly identified uses or recent increases in reported concentrations of use), or heightened public concerns warrant revisions to earlier conclusions. For example, lanolin-derived ingredients were prioritized following lanolin's designation as the "Contact Allergen of the Year" in 2023 by the ACDS, along with the availability of new toxicological information published since the prior CIR re-review in 2005.[9]

Ingredient Grouping and Read-Across Strategies. Over the past decade, CIR has increasingly incorporated ingredient grouping and read-across strategies as pragmatic tools for evaluating structurally-related cosmetic ingredients while minimizing reliance on new animal data. These approaches are based on the premise that structurally- and mechanistically-similar substances are likely to exhibit comparable toxicological profiles, and that data from well-characterized "source" chemicals can be judiciously used to fill specific endpoint data gaps for less-studied "target" chemicals within a defined group.

CIR's use of grouping began with small clusters, such as the initial review of three trimonium compounds nearly three decades ago, and has since expanded dramatically. In one landmark report, CIR assessed 369 alkyl PEG ether ingredients using a read-across framework that grouped substances with shared structural features (e.g., alkyl chains and polyethoxy repeat units).[10] More recently, the Expert Panel established a Read-Across Working Group (RAWG) to propose scientifically-defensible grouping schemes and to evaluate the confidence in read-across justifications on a case-by-case basis. As a technical subgroup, RAWG discussions are non-decisional and focus on identifying scientific strengths, limitations, and uncertainties to inform the full Panel's public deliberations. Importantly, CIR distinguishes between classical read-across and broader ingredient "family" reviews. Botanicals, other natural complex substances (NCS), other mixtures, polymers, and inorganics are often not amenable to classical read-across due to compositional complexity or limited mechanistic clarity. Nonetheless, such ingredients may still be reviewed as groups, providing useful inferences based on shared botanical species, plant parts, extraction methods, constituent profiles, routes of exposure, or other exposure mitigating factors (e.g., extremely large molecular weights). Assessing ingredients in families allows for efficiencies in time and resources while maintaining scientific rigor.

While read-across provides a powerful means of leveraging available data, it is not a substitute for robust direct evidence, particularly when addressing sensitive endpoints, structurally-complex substances, or cases in which exceptional toxicity mechanisms may apply. Read-across should therefore be conducted in a compound-specific and endpoint-specific manner that complements the WoE.

Phased Review Process: From Data Collection to Final Safety Assessment

Once an ingredient is placed on the finalized Priority List, CIR initiates an iterative process that advances from data compilation to final safety determination. The evaluation begins with preparation of the Scientific Literature Review (SLR), which summarizes available information on chemical identity, use concentration, toxicological data, and relevant clinical findings. Typical categories of data considered in CIR safety assessments are summarized in Box 2. The SLR is prepared by a CIR scientific analyst and posted online for a 60-day public comment period, during which time unpublished data and relevant comments may be submitted.

Box 2. Typical Data Needs for each Safety Assessment

- Chemical properties, composition and impurities, and method of manufacture
- Maximum concentrations per use conditions
- Toxicokinetics (ADME), especially dermal absorption and penetration
- Systemic repeated-dose toxicity data, including specific endpoints, e.g.,
  - Developmental & reproductive toxicity (DART)
  - Carcinogenicity, genotoxicity, mutagenicity, etc.
  - Rarely, other systemic toxicity endpoints (e.g., endocrine effects)
- Local effects, including
- Dermal
- Irritation and sensitization (i.e., type IV delayed hypersensitivity)
- Phototoxicity (including photo-allergenic effects)
- Inhalation/respiratory toxicity data (incidental exposure)
- Ocular irritation and other effects (incidental exposure)
- Mucous membrane toxicity for both intended (e.g., lipstick) and incidental exposures (e.g., bath)

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The Expert Panel convenes four times annually in sessions open to the public, both in-person and virtually. Meetings routinely include scientific briefings on emerging topics, such as advances in non-animal/alternative methodology testing, FDA perspectives on cosmetics versus drugs, and the application of current read-across methodologies to specific cosmetic ingredients. Meetings also include team-based deliberations, and plenary discussions in which the Panel reconciles differing perspectives and reaches consensus through formal voting. All meeting materials, including agendas, background packages (including submitted unpublished data), meeting minutes, briefing slides, and post-meeting announcements (PMAs), are published on the CIR website to ensure transparency.

Following the public comment period, the SLR is refined into a Draft Report (DR) that incorporates newly received information and is presented to the Expert Panel during a public meeting. The Panel evaluates the totality of the evidence, but does not conduct new experimental work. Although CIR staff compile and organize the data, they do not reach safety conclusions; interpretation and substantive decision-making rest solely with the Expert Panel.

If upon review of the DR no further data are needed to reach a conclusion of safety, the Expert Panel formulates a Discussion and issues a Tentative Report (TR). However, if the DR comprises insufficient evidence to support a safety determination, the Expert Panel issues an IDA specifying the additional information required. However, whether or not the requested data are received in response to the IDA, following a 60-day comment period the CIR scientific analyst then prepares a new iteration of the report (e.g., a draft TR if an IDA was issued or a draft Final Report (FR) if the data were sufficient and a TR for public comment was previously issued) for Expert Panel review at a subsequent meeting. Regardless of the path to a TR (i.e., through an IDA or not), it is at this stage that the Expert Panel will issue their first, tentative conclusion (i.e., safe, safe with qualifications, unsafe, or insufficient data). The Discussion section of each TR provides the rationale for the Panel's preliminary conclusion by describing any key data gaps, uncertainties, and scientific considerations underlying the assessment.

The CIR scientific analyst continues to chaperone the report through various iterations, meetings, and public comment periods, culminating in the presentation of a draft FR for Expert Panel consideration. Following consideration of any substantive comments or new information, the Expert Panel issues a FR that documents the rationale for its conclusion and cites all supporting data. FRs also reference relevant CIR resource documents—such as those addressing incidental inhalation exposure, epidemiological analyses of hair dye ingredients, and the heavy metals and impurities boilerplate, which standardizes the evaluation of trace contaminants (e.g., heavy metals and other impurities) that may be present in raw materials, particularly botanical derived ingredients. These resources provide detailed scientific context and elaborate the Panel's position on these specific issues.

Once an FR is issued, if the conclusion is insufficient data and no reported uses are identified in the RLD, the ingredient is classified as "No Reported Use" (with a meaning of use-not-supported on the basis of unknown use conditions; e.g., conclusions on 6-Amino-*o*-Cresol and Toluene-3,4-Diamine). If reported uses exist but sufficient data are not received within a 2-year period, the ingredient conclusion is converted from "insufficient data" to the "use not supported" category.

After each meeting, the CIR publishes any issued TR, FR, and accompanying PMA. The PMA summarizes the discussions and decisions of the Expert Panel and identifies any IDAs and associated data needs, when applicable. Each FR is made available in the CIR Reports database online, where anyone may freely download and utilize the report. Additionally, the National Institutes of Health, National Library of Medicine includes these reports as a data source in PubChem® (the world's largest collection of freely accessible chemical information); this means that anyone around the world may easily search and obtain these reports for free.

Each FR is also submitted as a manuscript for publication in *International Journal of Toxicology* (IJT). Once a peer-reviewed version of the report is published via *IJT*, it replaces the CIR version of the FR in the CIR Reports database (and in PubChem). Throughout this process, CIR maintains a policy of openness, transparency, and stakeholder engagement to ensure scientific credibility and sustain public confidence in cosmetic ingredient safety evaluation.

Re-Review and Continuous Updating of Safety Assessments

CIR operates under a policy of continuous review to ensure that safety assessments remain aligned with evolving scientific knowledge and conditions of use. Ingredients are typically re-evaluated on a 15-year cycle, although earlier re-review may be initiated in response to new data, new applications, or emerging safety concerns. During re-review, CIR staff conduct updated literature searches and exposure analyses and, when appropriate, apply read-across principles to group chemically-related ingredients. The Expert Panel may reaffirm prior conclusions, revise them in light of new evidence, or broaden the report to include additional closely-related ingredients.

If, following re-evaluation, the Expert Panel determines that reopening the assessment is unnecessary, the reaffirmation and its supporting rationale are recorded in the PMA and subsequently summarized in *IJT*. Alternatively, if the Expert Panel determines that reopening the assessment is appropriate, the process described above begins again with a

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draft amended report (DAR). Through this iterative approach, CIR safety reports remain living documents that evolve alongside advances in toxicological science, medicine, regulatory developments, and uses.

Continuous Data Monitoring and Iterative Evidence Integration

To ensure consistency and scientific rigor across safety assessments, the Expert Panel maintains a suite of reference documents (https://www.cir-safety.org/cir-findings) that synthesize evolving scientific knowledge across complex safety domains. These resource documents provide structured scientific frameworks that support systematic data monitoring, evidence integration, and interpretation. Through an adaptive process, scientific understanding is continuously reassessed, updated, and refined in response to emerging toxicological data, mechanistic insights, evolving exposure evidence, and international regulatory practice.

Respiratory exposure risk remains a major focus due to the increasing diversity of spray, aerosol, and powder cosmetic products. CIR's *Respiratory Exposure Resource Document* outlines a tiered framework for evaluating inhalation exposures that considers particle or droplet size, deposition behavior, physicochemical properties, formulation characteristics, and realistic consumer use conditions.[11] The Expert Panel continues to refine this framework by incorporating empirical aerosol characterization data and human-relevant deposition modeling, while also monitoring emerging formulation technologies that may influence inhalation exposure. While particle or droplet size is an important determinant, the Expert Panel recognizes that inhalation safety is also influenced by additional factors, such as the physicochemical properties of ingredients, in situ agglomeration, systemic and local toxicity (e.g., effects on the lung), and realistic exposure parameters (e.g., product type, frequency of use, and deposition efficiency). Since its initial release in 2012, this guidance has been periodically updated to incorporate advances in empirical aerosol characterization and human-relevant deposition modeling. The Expert Panel continues to encourage submission of product particle-size distribution data, particularly when formulations, delivery systems, or propellants change, and actively monitors emerging technologies, such as hybrid airbrush systems, dry shampoos, and nano-enabled propellant sprays, to ensure assessments reflect real-world exposure conditions. The tiered approach for calculating inhalation exposure to cosmetic spray products, originally proposed by CIR, has exerted a lasting influence on international inhalation safety assessment and is now recognized as a reference model by both regulatory authorities and the cosmetics industry.[12] By introducing a stepwise refinement process that progresses from conservative default assumptions to refined exposure modeling and experimental measurement, the CIR approach has significantly advanced the consistency, transparency, and scientific robustness of inhalation exposure assessments.

As hair dye formulations and consumer use patterns evolve, the Expert Panel continuously reviews epidemiological studies to evaluate the potential associations between personal hair dye use and cancer risk, ensuring that the conclusions remain protective and evidence based. The *Hair Dye Epidemiology Resource Document* provides a structured summary of key epidemiological data, categorized by study design and stratified by cancer type, with focus on studies published since approximately 2010.[13] The Expert Panel periodically updates its conclusions as new, high-quality evidence becomes available. In parallel, the Expert Panel recognizes the critical role of the endocrine system in reproduction, development, and overall physiological balance. *CIR's Precedents: Endocrine Activity* outlines how mechanistic, in vivo, and human observational data are integrated to evaluate potential hormone-related effects.[14] The Expert Panel carefully considers all available evidence to determine whether an ingredient exhibits endocrine activity that can be linked with potential adverse health outcomes.

For botanically derived ingredients, which are complex mixtures with compositions that vary by species, plant part, and processing, CIR develops a botanical boilerplate that standardizes scientific language and provides a structured framework for evaluating identity, composition, manufacturing methods, and potential contaminants (e.g., pesticide residues, heavy metals, mycotoxins). This internal resource enhances compositional transparency and supports consistent, systematic hazard and exposure evaluation of plant-derived cosmetic ingredients.

In addition, CIR maintains a number of topic-specific methodological references that ensure consistency across safety assessments. These include frameworks addressing margin-of-exposure (MOE) calculations, read-across strategy development, the evaluation of *N*-nitrosation potential in cosmetic products, and special safety considerations related to dermal absorption characteristics in infants and babies. Each document is refined through iterative expert review and stakeholder input to reflect current scientific and regulatory developments, ensuring that evaluation principles evolve in parallel with global scientific progress.

Collectively, these resource documents represent living frameworks that are regularly updated to incorporate new scientific findings, international guidance, and stakeholder input, supporting a dynamic, evidence-based approach to safety evaluation. Through continuous data monitoring and integration, CIR ensures that its safety assessments remain scientifically rigorous, transparent, and fully aligned with a modern, exposure-led, NGRA-compatible paradigm.

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Modernizing Safety Assessment: NGRA-Driven Evidence Integration, Exposure Focus, and Non-Animal Methodologies

Over the past decade, the CIR program has modernized its safety assessment framework while maintaining the core scientific approach that guides Expert Panel decision-making. CIR evaluations remain driven by clearly defined toxicological questions related to cosmetic exposure, such as whether an ingredient may cause sensitization, irritation, genotoxicity, systemic toxicity, or other adverse effects, and whether such effects pose a health risk under realistic conditions of cosmetic use. Within this endpoint-based evaluation structure, advances in regulatory science and the growing emphasis on human-relevant, exposure-informed risk assessment have led to the progressive incorporation of new tools and validated non-animal methodologies. While remaining grounded in traditional toxicology, CIR has increasingly adopted an exposure-led and evidence-integrated paradigm aligned with NGRA principles. This evolution reflects a strategic shift toward evaluating ingredient safety through structured problem formulation, tiered assessment, and transparent WoE integration, while continuing to ensure a high level of public health protection.

Evaluation of Data Sufficiency

CIR safety assessments are based on comprehensive reviews of all available scientific information relevant to cosmetic use scenarios. These include peer-reviewed literature, authoritative regulatory evaluations, international databases, and non-confidential data voluntarily submitted by stakeholders. Exposure scenarios considered by the Expert Panel encompass long-term (essentially lifetime), repeated use of cosmetic ingredients at maximum reported concentrations across relevant product categories. Use and concentration data are obtained through industry surveys conducted by the PCPC and, where appropriate, supplemented by regulatory listing data.

The Expert Panel evaluates the full spectrum of potential adverse health effects associated with cosmetic use, including systemic toxicity following repeated exposure, and integrates exposure and toxicokinetic information to inform internal dose estimates and support quantitative risk characterization. The assessment integrates findings from acute, short-term, and chronic toxicity studies conducted *in vivo* in mammalian species; *in vitro* studies using human or animal cells and tissues; *in silico* models (e.g., Derek); human clinical evidence; and epidemiological investigations that provide evidence of human relevance. Where validated NAMs are available, CIR incorporates NAM-based assessment strategies, such as Integrated Approaches to Testing and Assessment (IATA) and Defined Approaches (DAs), to support hazard identification and overall safety evaluation. When such approaches are not available or are insufficient to address specific endpoints, previously generated traditional animal data may also be considered as part of the WoE evaluation.

The assessment of data sufficiency takes into account several key considerations. These include the relevance of the data to human exposure and the route of administration, as well as the quality and reliability of the studies (e.g., whether the data are generated under validated OECD test guidelines or derived from limited screening assays). The consistency of findings across studies, including replication and the presence of dose-response relationships, is evaluated, and the biological plausibility of the observed effects is considered in the context of known mechanisms of action.

In accordance with CIR Procedures, no confidential or proprietary data are accepted, and all cited evidence must be publicly available or otherwise accessible for review. This principle ensures transparency, reproducibility, and third-party accountability across all stages of CIR's scientific review process.

Implementation of NGRA Principles in CIR Safety Assessments

CIR has increasingly aligned its safety evaluation practices with the principles of NGRA, a framework defined by the International Cooperation on Cosmetics Regulation (ICCR) that emphasizes exposure-led, hypothesis-driven, and human-relevant approaches to minimize animal use while maintaining scientific rigor and public health protection.[15] Each NGRA begins with a hypothesis linked to an exposure level or use scenario of the ingredient under evaluation. At the initiation of each ingredient assessment or re-review, CIR formulates a scientific problem statement that defines the safety questions and establishes an exposure-centered scope that encompasses relevant product categories, use patterns, exposure levels, and toxicological endpoints of concern.

Exposure assessments within CIR have evolved toward a more human-relevant, quantitative foundation via a tiered approach. Data inputs range from deterministic exposure estimates that apply conservative, health-protective assumptions to consumer habits and practices, to measured biomonitoring data in relevant human populations. At the initial tier, systemic exposure doses (SEDs) are derived from the PCPC's survey data on maximum use concentrations across current market product categories under the RLD, combined with realistic US population use patterns. These estimates can be further refined through the incorporation of empirical measurements into exposure assessment process. As a result, CIR's safety evaluations increasingly reflect NGRA principles by employing tiered and iterative approaches that progress from conservative default assumptions toward more refined, human-relevant exposure models. For

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example, to improve the accuracy of exposure estimates for Toluene as used in nail products, empirical measurements of Toluene concentrations in the breathing zone of women under simulated-use conditions have been incorporated to refine inhalation exposure models, thereby providing a more realistic basis for SED derivation and subsequent MoE calculation.[16] In addition, the Expert Panel has applied internal exposure metrics, such as plasma concentrations, to support SED estimation, and has begun exploring the application of PBK/PBPK modeling to further strengthen quantitative risk assessment.

These developments are consistent with emerging international scientific consensus, including deliberations by the EU SCCS, which recognize the conditional use of PBK/PBPK modeling and in vitro–to–in vivo extrapolation (IVIVE) as decision-relevant tools within NGRA, particularly in ab initio or animal-sparing assessments. While acknowledging remaining uncertainties, such approaches are considered informative when supported by transparent assumptions, fit-for-purpose in vitro ADME inputs, sensitivity and uncertainty analyses, and biologically plausible interpretation of internal exposure metrics. Accordingly, CIR considers such modeling outputs within an integrated, tiered WoE framework, rather than as stand-alone determinants of safety, and applies them in a manner commensurate with the regulatory question and available evidence.[17]

An essential feature of the NGRA framework is the systematic integration of information to support evidence-based safety decisions.[18] CIR applies a transparent WoE approach to systematically evaluate and integrate information from multiple sources, including in silico predictions, in chemico assays, in vitro and ex vivo reconstructed tissue models, legacy in vivo data, and human clinical or observational studies. When animal data are outdated or unavailable, NAMs may provide scientifically robust and ethically preferable tools for many aspects of hazard identification and risk characterization; however, their applicability remains endpoint-dependent. Validated NAMs are largely available for local and acute endpoints. For instance, the case study on acetyl glucosamine illustrates the application of NAM-based DAs (e.g., OECD TG 497) for skin-sensitization assessment, in which a combination of in silico, in chemico, and in vitro assays provided strong evidence for a non-sensitizing conclusion.[19] In contrast, NAMs addressing systemic and long-term toxicity are still under development and cannot yet replace full traditional datasets, without further substantiation within a WoE approach. Recent NGRA case studies involving coumarin, phenoxyethanol, and methyldibromo glutaronitrile (MDBGN) demonstrate that systemic toxicity can be explored using integrated bioactivity profiling, PBK/PBPK modeling, and high-throughput mechanistic assays; however, regulatory confidence and methodological maturity remain limited for stand-alone decision-making.[18,20-22] Consistent with recent NAM readiness evaluations, CIR recognizes that no single NAM is sufficient for complex systemic endpoints, and NAMs must be integrated through IATA/DAs and supported by internal exposure estimates to establish human relevance.

This integrated evidence base is structured and refined according to the initial problem formulation. At this stage, CIR defines the exposure scenario, identifies the relevant toxicological endpoints, and determines the level of refinement necessary to support a decision. This approach is exemplified in the evaluation of human repeated insult patch test (HRIPT) data.[19] The Panel recognizes that dose per unit area of skin is an important factor in interpreting HRIPT results and can support derivation of a No Expected Sensitization Induction Level (NESIL) using the QRA 2.0 (Skin Sensitization Quantitative Risk Assessment 2.0), taking into account cumulative exposure from diverse cosmetic products used over prolonged durations. To ensure safety, the Panel evaluates the concentration in HRIPT studies expressed as dose per skin unit area and, on a case-by-case basis, considers other factors that may affect test sensitivity and reliability, such as contact area, skin site permeability, and occlusion.

Through these practices, CIR has effectively translated NGRA principles into routine safety assessment workflows, establishing a tiered and iterative evaluation framework that integrates NAMs in a fit-for-purpose manner. This framework progresses from conservative, screening-level assumptions toward increasingly refined, human-relevant assessments as additional data and higher-quality evidence become available, ensuring that decision-making remains both protective and scientifically robust.

Modernizing CIR Practice Under NGRA: Advancing Toward an Animal-Sparing Framework

Over the past decade, CIR has steadily modernized its safety assessment framework, embracing a science-forward, human-relevant, and ethically progressive approach aligned with the principles of NGRA. While traditional in vivo toxicological data remain part of CIR's evidence base, increasing emphasis has been placed on integrating validated non-animal alternative methodologies, internal exposure metrics, and quantitative modeling to support safety decisions and reduce reliance on animal testing where scientifically justified. CIR's modernization reflects the deliberate incorporation of NAMs, integrated through approaches such as IATA and DAs, across hazard identification, exposure estimation, and risk characterization in favor of integrated tiered assessment strategies. This transition reflects CIR's adaptation to the global evolution of regulatory science, shifting from prediction-based toxicology toward protection-oriented assessment informed by mechanistic understanding (e.g., the application of AOPs) and human relevance. This framework reinforces CIR's dual commitment to scientific advancement and public health protection by prioritizing decision-making that prevents harm to consumers at relevant exposures, rather than relying on animal testing to predict toxicity where such data may not be necessary. During this process,

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the Expert Panel has paid particular attention to the progression of NGRA from conceptual frameworks to practical implementation, especially for endpoints related to systemic toxicity, where the availability and application of validated methodologies and regulatory confidence thereon continue to evolve.

To support this transition, CIR has also modernized its scientific communication and methodological documentation practices by clearly documenting legacy methodologies, improving traceability of safety conclusions, and engaging stakeholders earlier in the review cycle. The Expert Panel continues to actively monitor and engage with advances in non-animal testing methodologies. Recent scientific presentations exemplify this commitment. At the 166th Expert Panel meeting, Dr Don Bjerke, then Chair of the CIR Science and Support Committee, presented *"Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies,"* highlighting the application of DAs described in OECD Guideline 497 and ongoing developments in NAMs for skin sensitization.[19] The presentation emphasized the integrated use of in silico, in chemico, and in vitro methods, as well as the growing regulatory acceptance of these approaches by US agencies such as the FDA and Environmental Protection Agency (EPA). At the 169th Expert Panel meeting, Dr David Allen, Senior Director of the ICCS, delivered a presentation titled *"Identifying Eye Irritation Hazards Without Using Animals,"* briefing the Panel on the OECD-endorsed in vitro and ex vivo test methods and the US EPA's decision framework for non-animal evaluation of eye irritation and corrosion hazards.[23] Collectively, these initiatives illustrate CIR's continued efforts to enhance transparency, scientific rigor, and confidence in the application of non-animal methodologies. Further advancing this direction, at the 175th Expert Panel meeting, Dr Donna Macmillan of the ICCS introduced the 2025 ICCS Best Practice Guidance (BPG) for Skin Sensitization Assessment, which establishes a structured, stepwise framework for integrating NAMs into hazard identification and safety evaluation in alignment with NGRA principles and OECD frameworks.[24] The BPG provides practical tools for safety assessors shifting from traditional toxicology to NAM-based assessment, combining OECD-endorsed in chemico, in vitro, and in silico methods with exposure-based waiving strategies and quantitative interpretation using human-relevant metrics such as dose per unit area and margin of exposure.

As part of its broader modernization efforts, CIR has also critically reassessed the role of legacy assays and methodological references within its safety evaluations. In 2026, the Panel reviewed the evidentiary role of historical, obsolete, and non-standard genotoxicity assays in CIR safety assessments in light of updated OECD guidance and contemporary guideline-based approaches.[25,26] The Panel determined that results from obsolete assays, such as sister chromatid exchange, unscheduled DNA synthesis, and the *B. subtilis* Rec assay, are of limited interpretability. While citations to such studies may be retained for transparency to indicate that they were identified and considered during the review process, these studies are not relied upon in the overall WoE evaluation. This approach promotes consistency across CIR reviews and provides transparency to stakeholders regarding the evidentiary weight assigned to legacy data, thereby maintaining alignment with contemporary regulatory expectations.

At the same time, the Expert Panel has emphasized the growing importance of emerging NAMs that offer more human-relevant and predictive alternatives to animal testing, and support health-protective safety decisions. Consistent with this perspective, the Expert Panel has reaffirmed the application of a WoE approach that integrates findings from gene mutation, structural chromosomal aberration, and aneuploidy assays, with interpretations tailored to the specific dataset available for each ingredient under review. This framework allows CIR to remain scientifically robust while accommodating ongoing methodological advances. For instance, the OECD is currently advancing the ToxTracker reporter assay as a draft TG under public consultation,[27] and the 3D reconstructed skin micronucleus (RSMN) assay has recently been added to the OECD Work Plan for the TG Programme (Project 4.139),[28] both of which are being closely monitored by the Expert Panel.

CIR at 50: Achievements, Impact, and Path Forward

Since its inception in 1976, CIR has completed original safety assessments for more than 6000 individual cosmetic ingredients. Including original ingredient evaluations, re-reviews, and amended/revised reports that reflect newly available data, advances in analytical methodologies, evolving conditions of use, and updated safety conclusions, the number of ingredient conclusions issued by the Expert Panel is well over 7000. Over the past decade (2015 - 2025), CIR has issued more than 300 new or updated (i.e., re-reviewed) safety assessments, covering over 3000 individual ingredients. This progress reflects CIR's commitment to continuous process improvement and has been driven in part by the implementation of ingredient grouping and read-across strategies, which enable scientifically justified extrapolation/interpolation of data across structurally or toxicologically related substances. The distribution of final conclusions across all CIR safety assessments through June 2026 is summarized in Table 1.

Beyond the quantitative expansion of its assessments, the nature and transparency of CIR conclusions exemplify the program's evidence-based and risk-focused decision-making framework. Each CIR safety assessment culminates in a categorical conclusion that communicates the Expert Panel's judgment of safety under the intended conditions of use. A "safe-as-used" conclusion indicates a negligible risk of acute or chronic health effects under long-term, daily exposure at

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the highest reported use concentrations in cosmetic products when used as intended. The phrase "as used" specifically refers to the practices of use and maximum concentrations described in each report, reflecting the central role of real-world exposure in CIR's risk determinations. Among safe conclusions, the most frequent is "safe with qualifications" (e.g., when formulated to be nonirritating and/or non-sensitizing). Other common qualified findings include "safe with restrictions on ingredient concentrations" and "safe with limits on impurity levels." Conversely, ingredients such as 4-Methoxy-*m*-Phenylenediamine and its salts, Chloroacetamide, Ethoxyethanol and its acetate, HC Blue No. 1, and 4-Chloro-2-Aminophenol have been determined to be unsafe for cosmetic use. The Panel has also issued use-specific safety determinations for certain substances. For example, Formaldehyde and Methylene Glycol have been determined to be safe for use in nail products, safe with qualifications for dermal applications to ensure use at the minimal effective concentration, and unsafe in hair-straightening (hair-smoothing) products. Similarly, Hydroquinone and *p*-Hydroxyanisole have been determined to be safe for use in nail adhesives and in artificial nail coatings, but unsafe for use in other leave-on cosmetic products. When data are inadequate to support a definitive safety determination, the Panel issues an insufficient data conclusion and requests additional information. If the requested data are submitted and reviewed, the Panel re-evaluates the ingredient and may revise the conclusion to safe, safe with qualifications, or unsafe, depending on the weight of the new evidence.

In 2024, CIR advanced public access to its scientific findings by partnering with the US National Library of Medicine to integrate the CIR safety report database as a data source of PubChem®, a leading open-access platform for chemical information. This integration significantly enhances the visibility of CIR's evaluations, and facilitates use by regulators, researchers, and consumers worldwide. By enabling direct searches of CIR summaries alongside chemical identity, structural data, and toxicity information, this integration strengthens CIR's role as a transparent, globally-accessible source of cosmetic safety evaluation information.

CIR reports are referenced not only by US regulatory agencies but are also increasingly cited by authorities and expert committees internationally as part of their own ingredient safety substantiation and regulatory decision-making processes, such as the EU Scientific SCCS, Health Canada, the Korea Cosmetic Association (KCA) and the Korea Cosmetic Industry Research Institute (KCII), and the National Medical Products Administration of China (NMPA). The program's transparent methodology, rigorous WoE evaluations, and consistent publication in peer-reviewed literature have contributed to CIR's credibility as an internationally-respected source of ingredient safety information. In turn, CIR assessments—integrating both traditional toxicological safety evaluation and modern NAMs-based approaches—have informed ingredient approvals, risk evaluations, and harmonization initiatives within broader global cosmetic regulatory frameworks for cosmetic safety.

Looking ahead to its second half-century, the CIR program is poised to strengthen its alignment with modern safety evaluation paradigms—particularly the integration of exposure-based risk assessment, non-animal alternative methodologies, and NGRA principles—to further enhance human relevance and confidence in safety decisions while minimizing animal testing. Continued modernization of data integration tools, harmonizing with international frameworks developed by OECD, ICCR, ICCS and other global partners, and engagement with emerging scientific disciplines will ensure that CIR remains a global leader in cosmetic ingredient safety evaluation. The coming phase will see expanded use of validated NAMs, AOP-informed frameworks, and probabilistic exposure tools to refine internal exposure metrics. Consistent with global NGRA developments, CIR also anticipates broader incorporation of emerging exposure-based metrics, such as the Margin of Internal Exposure (MoIE) and internal TTC (iTTC). Additional advancements are expected to include the application of PoDs derived from alternative in vitro assays, as well as OECD-adopted DAs for diverse toxicity endpoints and curated databases to support evidence integration and efficient risk-based decision-making. In parallel, CIR will maintain its commitment to open-access scientific communication, ensuring that its evaluations remain accessible to regulators, industry stakeholders, and the public alike.

As CIR marks its 50th anniversary, it stands not only as a historic institution in cosmetic ingredient safety, but also as a

Table 1. Frequencies of Conclusions in CIR Safety Assessments Through June 2026

Conclusion	Number of ingredients	Percent distribution
Safe as used	2710	42.9%
Safe with qualifications	3199	50.6%
Insufficient data without current uses	13	0.2%
Insufficient data with current uses	233	3.7%
Use not supported	148	2.3%
Unsafe	16	0.3%
Total	6319	100%

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forward-looking model for scientific rigor, transparency, and adaptability. By embracing evolving methodologies, engaging with global partners, and prioritizing human-relevant, exposure-led assessments, CIR has positioned itself to meet the challenges of next-generation safety science. Through its promotion of non-animal testing strategies, transparent data sharing, and open scientific communication, CIR continues to play a leading and influential role in advancing global cosmetic safety science.

Author's Note

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Appendix

Abbreviations

AAD	American Academy of Dermatology
ACDS	American Contact Dermatitis Society
ADME	Toxicokinetics: absorption, distribution, metabolism, and excretion
AOP	Adverse outcome pathway
BPG	Best Practice Guidance
CFA	Consumer Federation of America
CFSAN	Center for Food Safety & Applied Nutrition
CIR	Cosmetic Ingredient Review
CTFA	Cosmetic, Toiletry, and Fragrance Association
DA	Defined Approach
DAR	Draft Amended Report
DART	Developmental and Reproductive Toxicity
Dictionary	*International Cosmetic Ingredient Dictionary*
DR	Draft Report
EPA	U.S. Environmental Protection Agency
EU	European Union
FDA	U.S. Food and Drug Administration
FOIA	Freedom of Information Act
GRAS	Generally recognized as safe
HCTC	Hair Color Technical Committee
HRIPT	Human repeated insult patch test
IATA	Integrated Approaches to Testing and Assessment
ICCR	International Cooperation on Cosmetics Regulation
ICCS	International Collaboration on Cosmetics Safety
IDA	Insufficient Data Announcement
IVIVE	In vitro-to-in vivo extrapolation
KCA	Korea Cosmetic Association
KCII	Korea Cosmetic Industry Research Institute
MBA	Master of Business Administration
MDBGN	Methyldibromo glutaronitrile
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MoE	Margin of Exposure
NAM	New Approach Methodology
NCS	Natural Complex Substances
NESIL	No Expected Sensitization Induction Level
NGRA	Next-Generation Risk Assessment
NMPA	National Medical Products Administration of China
OCAC	Office of Colors & Cosmetics
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-counter
PBPK	Physiologically based pharmacokinetic
PCPC	Personal Care Products Council
PMA	Post-Meeting Announcement
PoD	Point of Departure
QRA 2.0	Skin Sensitization Quantitative Risk Assessment 2.0
RAWG	Read-Across Working Group
RIFM	Research Institute for Fragrance Materials
RLD	Registration and Listing Database
SCCS	Scientific Committee on Consumer Safety
SED	Systemic Exposure Dose
SLR	Scientific Literature Review
SSC	Science and Support Committee
TG	Test Guideline
TR	Tentative Report
TTC	Threshold of Toxicological Concern
VCRP	Voluntary Cosmetic Registration Program
WoE	Weight of Evidence

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Words matter in toxicology and risk assessment as they impact risk communication

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Abstract

Clear, consistent language is essential in toxicology and risk assessment because terminology directly affects risk communication and understanding. The original concept of a "No Harm Dose of Reasonable Certainty" (NHDoRC) for an amount of chemical to which people can be exposed without detrimental effects is a plain language expression that clearly describes regulatory intent. However, the subsequent introduction and use of many related technical terms, such as NOAEL, BMD, RP, and PoD, with almost the same meaning, can confuse non-experts and even scientists working in different regulatory entities. Similarly, ADI, RfD, TDI, MRL, HBGV, and RV are all different abbreviations used in toxicology and risk assessment to describe the "acceptable" human dose in the context of food, water, and environmental chemicals. Likewise, the frequent use of terms such as margin of exposure (MoE) and margin of safety (MoS) interchangeably further complicates communication, as they are mathematically (and toxicologically) quite different. NOAEL and BMD_{10} are sometimes used interchangeably, but they usually represent two different points on the dose–response curve. Because of the many complications in the terminology used in risk assessment, a committee should be established to harmonize terminology across agencies and the wider risk assessment community, including industry and academia. The recommendations from such a committee would improve clarity, transparency, regulatory efficiency, and public trust in chemical risk assessment.

Key words: risk assessment; risk communication; harmonization

Abbreviations: ADI: Acceptable Daily Intake; **ADME:** Absorption, Distribution, Metabolism and Excretion; **BMD:** Benchmark Dose; **BMDL:** Benchmark Dose lower confidence limit; **BMD_{10}:** Benchmark Dose 10%; **HBGV:** Health-Based Guidance Value; **HHRV:** Human Health Reference Value; **$NOAED_{lab\ anim}$:** No Observed Adverse Effect Dose in laboratory animals; **MoE:** Margin of Exposure; **MoS:** Margin of Safety; **MRL:** Minimal Risk Level; **$NHDoRC_{human}$:** No Harm Dose of Reasonable Certainty for humans; **NOAEL:** No Observed Adverse Effect Level; **PoD:** Point of Departure; **QSAR:** Quantitative Structure Activity Relationship; **RfD:** Reference Dose; **RP:** Reference Point; **RV:** Reference Value; **TDI:** Tolerable Daily Intake; **UF:** Uncertainty Factor.

Discussion

One of the goals of regulatory agencies is to protect public health. In the case of chemicals, they do this by performing toxicological risk assessments. Some people refer to the subjects of these assessments as "agents." However, "Chemicals" is the preferred term because "agents" in common parlance frequently refers to those individuals employed by agencies, such as the Federal Bureau of Investigation (FBI), Komitet Gosudarstvennoy Bezopasnosti (KGB), US Immigration and Customs Enforcement (ICE), and the like. The word "agents" is appropriate when discussing radiation and chemical warfare agents. There is also confusion between the words "toxins" and "toxicants". "Toxins" are produced by biological organisms, such as plants, animals, fungi, etc., whereas "toxicants" are synthetic, human-made, toxic chemicals. (The discussion below is restricted to non-carcinogenic chemicals.)

Regulatory agencies conduct risk assessments to determine a "No Harm Dose of Reasonable Certainty ($NHDoRC_{human}$)" for individual chemical exposures for humans and communicate this to the public. The standard for the "No Harm Dose of Reasonable Certainty" originally used by Lehman and Fitzhugh is called "Reasonable Certainty of No Harm" in various FDA documents, and in Europe the equivalent wording is "Without Appreciable Risk to Health." It is unfortunate that the term NHDoRC, first used by the "fathers of risk assessment", Lehman and Fitzhugh (1954), has not continued to be the predominant term in risk assessment because these words explicitly describe the goal of risk assessment, and the use of plain language makes its meaning easily understood. The NHDoRC usually applies to humans and not laboratory animals; therefore, to eliminate any potential confusion, the word "human" probably should be added to the abbreviation as a subscript "$NHDoRC_{human}$." Unfortunately, different words have largely replaced the "$NHDoRC_{human}$" in risk assessment. One of such frequently used terms is "safe dose", even though it is impossible to determine a safe dose in animals or even in humans. This is why the term "risk assessment" is used rather than "safety assessment". As strange as it might be, even a few thousand humans used in clinical trials may not serve as the best model to determine the safe dose of a chemical, such as a drug, for the entirety of the human population. This becomes evident when a newly approved drug is prescribed, and hundreds of thousands or millions of patients are

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exposed to that drug. Sometimes, serious adverse effects may manifest in some individuals; this is often due to rare or otherwise unaccounted inter-individual genetic variations. When risk assessors use the word "safe dose", they really mean a dose of a chemical that has reasonable certainty of no harm, as first defined by the US FDA decades ago. However, this is not widely recognized by the public, and the inference of absolute safety has become widespread.

This rationale and process for regulating chemicals in the United States was first used for food additives but has expanded to many other regulatory areas in the United States including cosmetics, environmental chemicals, pesticides, etc. The testing paradigms and methods have also been adopted by most countries globally, as well as by the World Health Organization and its committees. They have stood the test of time for over 75 yr. A series of books published by the US National Academy of Sciences has remained a hallmark publication in this regard (National Research Council (NRC) 1983, 1994, 2009). The risk assessment paradigm and testing methods are also discussed in the FDA's Redbook 2000, which was revised in 2007 (US Food and Drug Administration (FDA) 2007), by the Food and Agriculture Organization of the United Nations (FAO), and by the World Health Organization (WHO) in the Environmental Health Criteria (EHC) 240 in 2009 and its updates (2020).

Terminologies used to describe how the highest dose of a chemical producing no adverse effects in laboratory animals is determined

Regulators for chemicals other than pharmaceutical products often have little or no data from humans to determine the dose with a reasonable certainty of no harm. This is true for many chemicals in our food, most chemicals used in industry, cosmetics, and agriculture. A two-step process is used to determine whether these chemicals have a reasonable certainty to produce no harm in humans. Currently, and in most regulatory domains, the first step is to perform experiments in laboratory animals, although there is a desire to use non-animal methods. Testing in animals for cosmetics and cosmetic ingredients has been banned in Europe and some states in the United States. The laboratory animals are exposed to the route by which humans are likely to be exposed. For chemicals in our food, including pesticides, the chemical is added to the feed or water of rats and/or mice at generally three or four concentrations (including a zero-exposure "control group") for 90 or more days. For cosmetics, the route of administration is routinely the skin and eye, as appropriate, and for other industrial chemicals, they are also added to the air that the animals breathe. Chemical exposures are often continued over the lifespan of the animals to determine chronic toxicity and carcinogenicity potential (approximately 2 yr in rodents). At the end of exposure to the chemical, many tests are employed, such as blood tests and histopathology of a broad spectrum of potential target organs. In addition, reproductive and developmental studies, a battery of genotoxicity tests, as well as specialized immunotoxicity, neurotoxicity, and endocrine-related tests are needed.

In addition to these toxicity tests, an additional battery of tests is conducted to characterize potential short-term "acute" toxicity potential, including determinations of acute lethal doses, eye and skin irritation, and sensitization potential. Toxicity tests are generally designed to include dose(s) not expected to induce any evidence of toxicity in the test animals, with the higher doses producing clear evidence of toxicity that compromises overall animal health.

Data from these laboratory animals exposed to various doses of a chemical and periods of exposure are used to determine the potential adverse effects of the chemical, also referred to as the "hazard." Thus, hazard identification does not focus on the dose of the chemical required to produce the effect. However, the dose-response of the hazard is important for determining the "risk," in which the dose required to produce the adverse effect of the chemical is considered. Unfortunately, these two most basic words in risk assessment are not differentiated by the public, and sometimes not even by scientists (Scheer et al. 2014). Risk is when the dose required to produce the adverse effect of the chemical is considered, in the context of a specific exposure scenario(s).

These animal studies also provide information on the highest dose of the chemical that does not produce any toxicity in the laboratory animals. This is often referred to as the "No Observed Adverse Effect Level (NOAEL)." It would probably be better to refer to this as the "No Observed Adverse Effect Dose ($NOAED_{lab\ anim}$)," as it was originally named, and a term for plain language communication. This suggested abbreviation indicates that it is not any dose that does not produce an adverse effect, but is the maximum dose (of those tested) that does not produce an adverse effect. However, at the $NOAED_{lab\ anim}$, some effects may still be observed, but those are usually not considered toxicologically relevant, such as a small increase in cytochrome P-450s. There might be more than one adverse effect, thus more than one dose response curve. However, the $NOAED_{lab\ anim}$ is determined only from the adverse effect observed from the lowest dose-response curve.

The abbreviation incorporates "lab anim" to indicate that the data originate from testing in laboratory animals, and it is a "dose" (usually the amount per kg body weight) and not a "level". In science, it is best to use words that are least likely to be misinterpreted, and dose, the most important word in toxicology, is preferred over level. The same logic applies to using the word "concentration" (typically amount per unit of feed or water) rather than "level", however the word "concentration" is appropriate for inhalation and topical exposures. The word "level" has various meanings when used in other contexts, which can lead to confusion when communicating to audiences outside of risk assessment. The dictionary indicates that "level" means a tool or measurement to determine whether the surface is perfectly horizontal and hence is readily open to misinterpretation.

There have been some refinements to determine a $NOAED_{lab\ anim}$ during the last 75 yr, such as the mathematically determined Benchmark Dose/Concentration ("BMD/BMC"), for a specified response. The "BMD" is the amount of a substance that produces a clear, specified, low-level health risk, usually in the range of a 1%–10% change in a specific toxic effect such as liver injury (EFSA Glossary). The "BMDL" is the 95% lower limit of the BMD and is closer to the $NOAED_{lab\ anim}$. The BMD approach has the advantage that it utilizes the entire dose response. Furthermore, the calculation of a BMD allows the setting of upper and lower confidence levels, thereby describing uncertainty with the dataset (Crump 1984; US Environmental Protection Agency (EPA) 2012; Haber et al. 2018; Faustman 2019; More et al. 2022). A disadvantage of the BMD approach is that the number of available data points is often less than desirable to determine the slope and shape of the line, and thus, the BMD cannot be used for all sets of data. The BMD approach was developed as an alternative to the $NOAED_{lab\ anim}$ or the NOAEL; thus, it might be better to indicate

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that the $NOAED_{lab\ anim}$ was determined by using BMD methodology. However, BMD and $NOAED_{lab\ anim}$ are not identical, as BMD is a dose that produces some adverse effect, whereas the $NOAED_{lab\ anim}$ does not produce an adverse effect in the study.

Adding to the confusion with risk assessment terminology, terms such as reference point (RP) and point of departure (PoD) (Aurisano et al. 2023) are often used as generic terms to indicate the $NOAED_{lab\ anim}$ (NOAEL), LOAEL, and BMD. It can be confusing when RP or PoD is used for three different points on a dose-response curve.

Terminology to describe how a No Harm Dose of Reasonable Certainty for humans ($NHDoRC_{human}$) is determined

In some special cases, observations in humans (e.g. occupational cohorts) may help identify hazards and calculate risks for the general human population. However, in most cases, we do not have sufficient human data and thus resort to laboratory animal studies. The first step in the risk assessment process, as described above, uses classical experiments in laboratory animals to determine the $NOAED_{lab\ anim}$. The second step is to extrapolate the data from laboratory animals to humans, which often requires the use of a "policy-driven" default uncertainty factor (100), except when sufficient data are available to aid in the extrapolation from animal data to humans.

In 1954, when Arnold Lehman and O. Garth Fitzhugh were developing regulations for contaminants and colorants in human food at the US-FDA (Lehman and Fitzhugh 1954), they prudently decided that the policy for the extrapolation of the $NOAED_{lab\ anim}$ to humans should employ an "uncertainty factor (UF)" of 100 to assure a "No Harm Dose of Reasonable Certainty ($NHDoRC_{human}$)." They specifically wrote "that the additive should not occur in human food in a quantity that is more than 1/100th of the amount of the maximum safe dose in animals". Thus, the policy of "acceptable risk" in humans was established as the "safe dose" in laboratory animals divided by 100. It is generally considered that the 100-fold uncertainty factor is to theoretically account for 10-fold interspecies variation and 10-fold for human variation. These 10-fold factors are also not experimental science but policy. Lehman and Fitzhugh stated (quoted as is), "the 100-fold margin of safety is a good target but not an absolute yardstick as a measure of safety. There are no scientific or mathematical means by which we can arrive at an absolute value. However, this factor of 100 appears to be high enough to reduce the hazard of food additives to a minimum and at the same time low enough to allow the use of some chemicals which are necessary in food processing. Since man can seldom be used as an experimental subject, reliance for the evaluation of the toxicity of a substance must ordinarily be placed upon studies in laboratory animals. Even then it cannot be said for certain that lack of toxicity in animals will necessarily forecast what may occur in man. However, the selection of the 100-fold margin of safety serves as a reasonable safeguard to minimize the danger". Retrospective analysis has shown that this was not an unreasonable choice (Hattis et al. 1987; Calabrese et al. 1992; Renwick 1993; Hattis and Silver 1994; Renwick and Lazarus 1998; International Programme on Chemical Safety (IPCS) 2005; US Environmental Protection Agency (EPA) 2014).

However, one should not conclude that chemicals are necessarily more toxic in humans (10-fold) than in laboratory animals; for example, one of the most toxic chemicals, dioxin (TCDD), is about 50 times more toxic to laboratory animals than humans (Connor and Aylward 2006; Eaton et al. 2024) or that a sensitive human varies 10-fold from an average human. The values were chosen to maximize the likelihood of human protection. However, when additional data are available regarding species differences between laboratory animals and humans in the toxicokinetic and toxicodynamic properties of chemicals, the UF can be reduced. For instance, an UF of 1 was selected for 2-butoxyethanol (EGBE) to account for the uncertainty associated with interspecies differences between laboratory animals and humans (US Environmental Protection Agency (EPA) 2010).

The no harm dose of reasonable certainty for humans ($NHDoRC_{human}$) is determined by dividing the no observed adverse effect dose in laboratory animals ($NOAED_{lab\ anim}$), as suggested by Lehman and Fitzhugh, with an uncertainty factor of 100.

$$NHDoRC_{human} = \frac{NOAED_{lab\ anim}}{100}$$

Risk assessments presently divide the NOAEL or BMD_{10} (or BMDL) by the uncertainty factor of 100, although the uncertainty factor may be higher or lower depending on the study duration or quality. However, as noted above, NOAEL and BMDs are different points on the dose-response curve, with the BMDL closer to the NOAEL than the BMD_{10}.

Possibly even more confusing than the multiple terms used to describe the "safe" dose for a chemical in laboratory animals are those used to describe the "acceptable risk" dose for humans. Some of these terms were established due to the classes of chemicals that various agencies were regulating and have some associated nuances in their interpretation. These terms used for the "$NHDoRC_{humans}$" include the acceptable daily intake ("ADI"), minimal risk level ("MRL"), tolerable daily intake ("TDI"), reference dose ("RfD"), and upper limit ("UL"). Another, more generic term, health-based guidance value ("HBGV"), has entered the literature of risk assessment from the early 2000s. The equivalent term sometimes used in Europe is Reference Value ("RV") or Human Health Reference Value ("HHRV") (Woodall et al. 2025). Both are umbrella terms that include ADI, TDI, RfD, UL, etc., and describe the maximum acceptable exposure in food/water for humans. The use of these numerous terms may carry a specific meaning among toxicologists and regulatory scientists when discussing chemical safety; however, it is likely to be confusing for individuals without specialized knowledge in the field. Thus, the adage "Keep It Simple, Stupid" ("KISS") might be appropriate; probably one term to communicate a concept is better than many.

Terminologies used to describe the margin of exposure and the margin of safety

An even larger problem in communication is when words mean different things to different people. For example, two additional terms have emerged from the original formula for calculating the $NHDoRC_{human,}$ namely the margin of exposure ("MoE") and the margin of safety ("MoS"), as used in the context of food safety.

The MoE is defined as the $NOAED_{lab\ anim}$ divided by the $Exposed\ Dose_{human}$, with a desired MoE of at least 100 (equivalent to the uncertainty factor described above). The formula for determining the MoE is shown below:

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$$\text{MoE} = \frac{\text{NOAED}_{\text{lab anim}}}{\text{Exposed Dose}_{\text{human}}}$$

In contrast, to calculate the MoS, the $\text{NHDoRC}_{\text{human}}$ is divided by the Exposed $\text{Dose}_{\text{human}}$ as shown below.

$$\text{MoS} = \frac{\text{NHDoRC}_{\text{human}}}{\text{Exposed Dose}_{\text{human}}}$$

While the term MoE is usually used correctly, there is much confusion about the use of the term MoS. The European Food Safety Authority (EFSA) clearly defined MoS as follows: "The margin of safety is the ratio between…the 'health-based guidance value' such as an ADI…and the actual or estimated exposure" (European Food Safety Authority (EFSA) 2023). The same definition is used in EHC 240 by FAO/WHO (2020). EFSA (2023) has also noted that MoS and MoE are two different concepts but are sometimes mistakenly used interchangeably. In the context of using words inappropriately, a MoE of 100 is sometimes misinterpreted as a 100-fold margin of safety (MoS). A recent publication (Bennekou et al. 2025) has concluded that MoE should be the metric used in safety assessments by EFSA.

Figure 1 shows the relationship between MoS and MoE. As noted in the figure, the $\text{NHDoRC}_{\text{human}}$ is 1/100th of the $\text{NOAED}_{\text{lab anim}}$. Three Exposed $\text{Dose}_{\text{human}}$ are shown; Exposed $\text{Dose}_{\text{human}}$-1 is lower than the $\text{NHDoRC}_{\text{human}}$ making the MoS > 1.0, which is desirable. Exposed $\text{Dose}_{\text{human}}$-2 is the same as $\text{NHDoRC}_{\text{human}}$ and thus the MoS = 1.0, which means there is still reasonable certainty of no harm because the Exposed $\text{Dose}_{\text{human}}$ does not exceed the $\text{NHDoRC}_{\text{human}}$. Exposed $\text{Dose}_{\text{human}}$-3 is higher than the $\text{NHDoRC}_{\text{human}}$ making the MoS < 1.0 and thus is not in the realm of reasonable certainty of no harm, because Exposed $\text{Dose}_{\text{human}}$ exceeds the $\text{NHDoRC}_{\text{human}}$.

Additional terminologies after analytical chemistry became an important part of risk assessment

The discipline of toxicology has often been divided into two areas regarding organism-toxicant interactions: one is what the body does to the chemical, that is, "toxicokinetics," and the other is what the chemical or metabolite does to the body, that is, "toxicodynamics." Thus, the studies described above were toxicodynamic, that is, what the chemical does to the animal. To determine the toxicokinetics of a chemical, one requires analytical techniques sufficiently sensitive to quantify the concentrations of chemicals in laboratory animals, which were not available during the early days of risk assessment. The advances in analytical chemistry have aided our understanding of the distribution of xenobiotics to tissues (dosimetry), improvements in understanding the metabolism of xenobiotics, as well as the various sources of exposure to the xenobiotic.

From the analysis of the chemical and its metabolites in the tissues and excreta of the exposed animals, one can then utilize this information to understand the absorption, distribution, metabolism (biotransformation), and excretion of chemicals, for which the acronym "ADME" is commonly used. It is unfortunate that "lab anim" was not attached to the acronym ADME, such as "$\text{ADME}_{\text{lab anim}}$," to avoid confusion between laboratory animal and human studies. All risk assessments should include ADME studies as they aid markedly in interpreting toxicological findings and are especially critical in determining whether the parent chemical or a metabolite, as well as the distribution of the chemical, are important in producing toxicity. In other areas of toxicology, there is some confusion about the use of ADME. Some people use the word elimination instead of excretion for the E in ADME. A chemical can be eliminated in two ways from the body: by metabolism and/or excretion. Therefore, the E in ADME should be used only for excretion.

How toxicokinetics is used in risk assessment

When the ADME of a chemical is determined at multiple time points after administration, one can determine the rates or kinetics for the ADME processes of the chemical. Toxicokinetics are very important in considering differences between species, doses, ages, etc. By determining the internal tissue dose of the chemical, they aid in deriving chemical-specific adjustment factors to replace default uncertainty factors. Toxicokinetics have provided a substantial refinement in risk assessment (International Programme on Chemical Safety (IPCS) 2005; US Environmental Protection Agency (EPA) 2014). The most common factor that alters kinetics between species and sexes is metabolism. It has been suggested by some to use the word kinetics or biokinetics to describe the disposition of a chemical with time. However, it is generally agreed that when kinetic data are being used to understand and explain the pharmacological actions of a

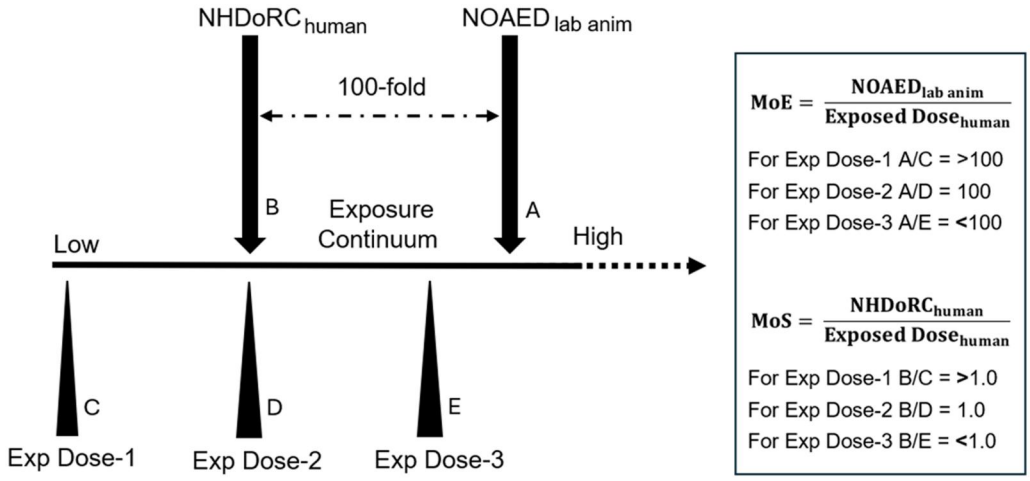


Fig. 1. Relationship among $\text{NOAED}_{\text{lab anim}}$, $\text{NHDoRC}_{\text{human}}$, Exposures human, MoE, and MoS in an exposure continuum. Exp Dose = Exposed $\text{Dose}_{\text{human}}$.

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drug, the word "pharmacokinetics" is more appropriate, but when describing the kinetics of a chemical to understand and explain adverse (toxicological effects), it is more appropriate to use the word "toxicokinetics." Unfortunately, these two terms are often used interchangeably. Also, the term toxicokinetics should not be used if ADME was only determined at a single time point, because kinetics refers to changes over time (rates).

Terminologies used when important data are missing for conducting a risk assessment

There is rarely as much toxicological and analytical data available for a risk assessment as one desires. One method that is used to overcome this problem is to evaluate the toxicology data of a chemical(s) that have a similar chemical structure and/or other key properties, and to use the data from this similar chemical that is not available for the chemical of interest. This type of comparison was originally referred to as "Quantitative Structure Activity Relationships (QSARs)," which might be understood by the lay community, but has been replaced by the more formalized term and approach, "Read-Across," which has minimal inherent meaning to the public. Read-across not only uses QSAR but additional tools, such as direct comparison to similar known chemicals, to predict the toxicity of a chemical (Lizarraga et al. 2023). The use of read-across to draw a safety conclusion might underestimate the risk of using the chemical, as many important uncertainties remain. Where possible, such data should be used to complement the overall toxicology data package, even if the data are limited. Read-across has many exceptions, as noted from a few examples. (i) If Lehman and Fitzhugh had used read across to do a safety assessment of hexane 75 yr ago, they would have concluded that it has relatively low toxicity because similar chemicals such as propane, butane, and heptane are relatively nontoxic, however it was discovered later that hexane is a potent neurotoxicant, due to peculiarities of its metabolism (Agency for Toxic Substances and Disease Registry (ATSDR) 2025; Bruckner et al. 2019; Yamamura 1969). (ii) Many aromatic hydrocarbons have similar chemical structures but have marked differences in their affinity for the aryl hydrocarbon receptor and consequent toxicity (Poland and Knutson 1982; Nebert 2017; Di Giulio and Newman 2019; Lehman-McKeeman 2019; Garland et al. 2020; Shankar et al. 2020). (iii) It is well known from drug development that a minor alteration in the structure of a chemical can markedly change its effect or its potency. A classic example is the difference in potency between some stereoisomers, which have very similar chemical structures. One may be a very potent drug, whereas the other may be totally inactive with respect to the specific pharmacological effect, such as L-DOPA (drug) vs D-DOPA. (iv) Vitamin A and its retinol/retinoid derivatives have different affinities for the RAR and RXR receptors and thus markedly different dose responses for producing teratogenic effects (Petkovich and Chambon 2022). (v) Another example is ethylene glycol that is highly toxic when ingested, versus propylene glycol that is well-tolerated with minimal toxicity and is used safely in food and drugs. Thus, the use of read-across should be undertaken with caution, particularly when dealing with novel chemicals, chemicals with bioactive versus inactive enantiomers, and chemicals that produce toxicity via receptor binding or other allosteric binding sites. Guidance documents have been developed over the last decade or so to help guide these activities and avoid some of the pitfalls noted (Organisation for Economic Co-operation and Development (OECD) 2007; Blackburn and Stuard 2014; Ball et al. 2016; European Chemicals Agency (ECHA) 2017; Patlewicz et al. 2018; Schultz et al. 2019). It would be gratifying if the term read-across could be replaced with one that has some inherent meaning to the public as well as to scientists other than toxicologists.

Read-across discussed above is considered a Non-Animal Method. The Tox 21 initiative accelerated the development of various Non-Animal Methods. The Toxicity Testing in the 21st Century (Tox 21) initiative of the National Research Council (NRC) of the U.S. National Academies (2007) recommended the development and use of new approaches, such as *in vitro*, omics, *in-silico*/computational approaches to evaluate chemical safety without relying on animal testing. The recommendation is to rely primarily on *in vitro* studies using human cells, tissues, and related human-relevant biological systems. These later became known as New Approach Methodologies (NAMs). The aim of using Non-Animal Methods in toxicology goes back over 60 yr to the principles of "3Rs" (Replacement, Reduction and Refinement). First proposed by Russell and Burch (1959), the concept of the 3Rs became widely influential from the 1980s as animal welfare science and regulations expanded. Thus, the concept of moving away from animal studies is not new, but the new acronym NAM is often interpreted as new and novel. The term "NAM" has different meanings for different people; for example, to some it means New Approach Methodologies, while to others it means Non-Animal Methods. Some include advanced transgenic mammalian models in the definition of NAMs, while others exclude these and all in vivo animal tests in vertebrates. Just like the term "read-across", the meaning of "NAM" is not obvious. Agreement is needed on a plain language expression for this that is suitable for effective communication to a wide audience.

Terminologies used to summarize the toxicology database for risk assessment

In the last century, Gregus and Klaassen (1996) in the Casarett and Doull textbook were probably the first to attempt to present an up-to-date, comprehensive toxicology framework, which they called "Mechanisms of Toxicity." Mechanisms provide the molecular, biochemical, physiological, pharmacological, and pathological basis of how toxic responses occur. This chapter has been updated in subsequent editions of the Casarett and Doull Toxicology textbooks, most recently in the nineth edition (Lehman-McKeeman 2019). This expanded view of toxicology divides the process into 4 steps: (i) delivery, (ii) interaction with the target, (iii) cellular dysfunction, and (iv) disrepair, which incorporates numerous mechanisms at each step and is depicted in Fig. 2.

Around the same time, a related concept, the Mode Of Action ("MOA"), was developed by the US Environmental Protection Agency (EPA) (2005) and the International Programme on Chemical Safety (IPCS), World Health Organization (2007), initially for chemical carcinogenesis but later extended to cover all toxicological effects. A similar framework was developed by ecotoxicologists (Villeneuve et al. 2014a, 2014b; Ankley and Edwards 2018), which is referred to as Adverse Outcome Pathways ("AOPs"). MOA and AOP are usually generalizations of a couple of steps in the mechanisms of toxicity. The AOP terminology has been extended to human chemical risk assessment and has become more widely used, even though it was introduced later and is less intuitive than the plain language term mechanisms of toxicity. For example, the term adverse outcome pathway most likely will mean to a layperson that the purpose of the pathway is

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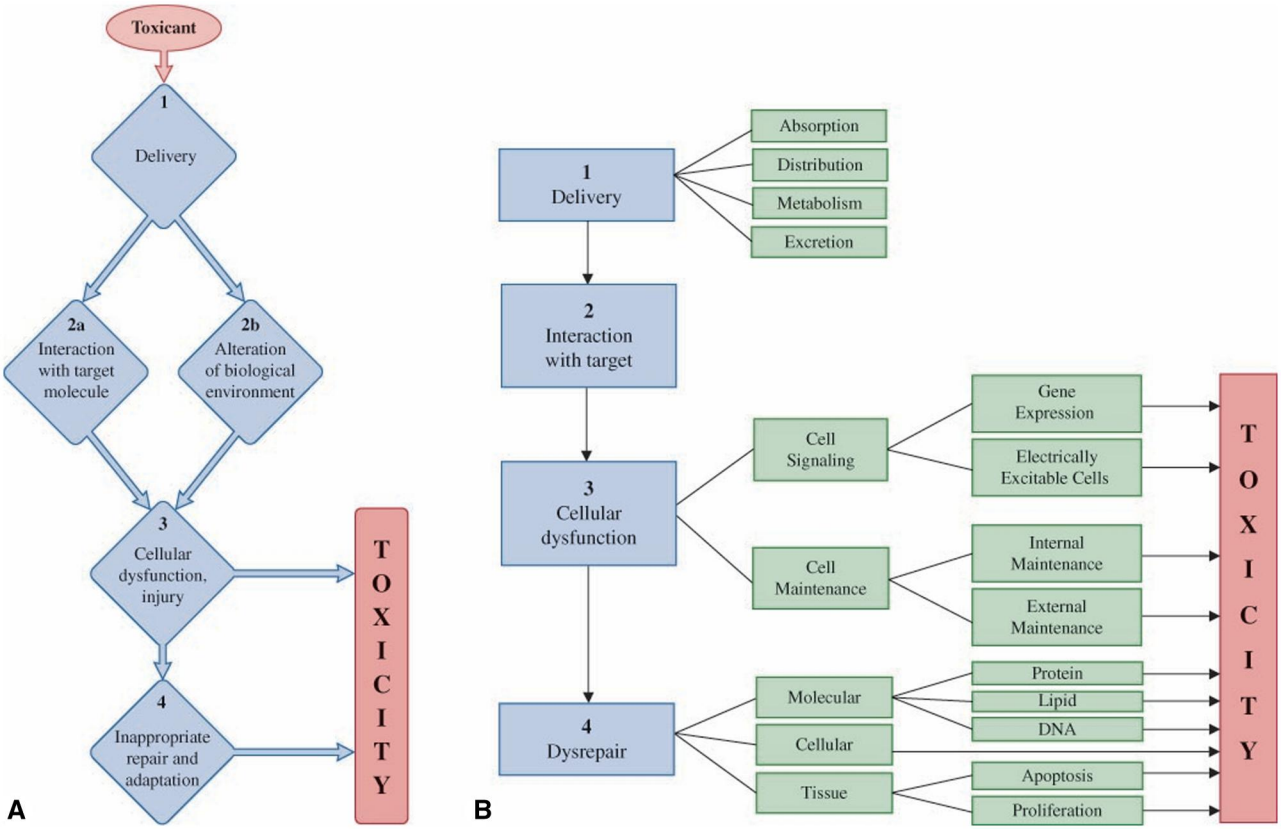


Fig. 2. Mechanisms of toxicity in 4 steps: (i) delivery, (ii) interaction with the target, (iii) cellular dysfunction, and (iv) disrepair, which incorporates numerous mechanisms at each step. From the nineth Edition of Casarett and Doull's Toxicology (ed. Curtis D. Klaassen) (Lehman-McKeeman 2019).

to mediate adverse effects, but these pathways are normal cellular pathways that, when perturbed, may result in toxicity. The AOP emphasizes portions of the pathway that are termed "Key Events." What is a key event, is not every step that a chemical undergoes, as in Fig. 2, a key event in producing a toxic effect? Absorption is seldom considered a key event, but without absorption there is usually no toxicity.

Conclusions

The goal of this article is to raise awareness that words matter in toxicology and can seriously impact risk communication and understanding. Hence, it is extremely important that toxicologists are careful with the words they use when interacting with the public and indeed with other non-specialists. It is unfortunate that scientists use multiple names for the same concept, as this is often confusing to laypeople and sometimes even to other scientists. We should make sure, before coining terms or acronyms for a concept, that one does not already exist. Most important is that we do not use terms in a way that could be confusing to many, as was demonstrated for MoS.

Harmonizing toxicology and risk-assessment terminology is essential for clarity, consistency, and public communication. Do we need numerous terms to represent the same concept? Do we need NOAEL, BMD_{10}, BMDL, PoD, and RP, which are often used interchangeably even when they are not the same, or could they be replaced by no observed adverse effect dose in laboratory animals ($NOAED_{lab\ anim}$), which has inherent meaning? Similarly, do we need ADI, TDI, RfD, MRL, and HBGV, which are sometimes used interchangeably even when they are not the same, and create confusion for regulators working in different agencies, as well as researchers and stakeholders, which raises the question of whether they might be replaced by $NHDoRC_{human}$, which the fathers of risk assessment coined? When vocabulary differs across agencies, comparisons become difficult, and communication is less transparent. Harmonized terms would streamline risk assessment, reduce misinterpretation, and improve the efficiency of regulatory decision-making. Ultimately, consistency in terminology enhances the credibility and accessibility of toxicology for both experts and the public. Harmonization of nomenclature for drug metabolizing enzymes, transporters, receptors, etc. has already greatly benefited researchers; for example, there was a time before such harmonization when various research groups were working on the same protein without realizing this, so that the findings were not integrated until later. So, why not harmonize risk assessment terminologies for consistency, transparency, and more effective risk communication?

It is difficult to persuade people to use correct terminology, to use someone else's terminology, and especially to change from the terminology they have used for years. It is said that scientists would rather use someone else's toothbrush than use someone else's terminology. However, we are doing toxicology and the public a disservice without such harmonization. The recommendations from a committee on chemical risk assessment terminology would improve clarity, transparency, regulatory efficiency, and public trust in chemical risk assessment.

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Forum

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice Fiume, M.B.A.
Senior Director, CIR
Date: September 25, 2026
Subject: Wave 2 - Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Amended Report on 2-Bromo-2-Nitropropane-1,3-Diol (*PCPCcomments_2-Bromo-2-Nitropropane-1,3-Diol_Wave2_102026*). Please note, the comments are largely editorial in nature.

Personal Care Products Council

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Jaap Venema, Ph.D.
EVP and Chief Scientist – Personal Care Products Council
Industry Liaison to the CIR Expert Panel

DATE: September 18, 2026

SUBJECT: Draft Final Amended Report: Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics (October 2026 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft final amended report, Amended Safety Assessment of 2-Bromo-2-Nitropropane-1,3-Diol as Used in Cosmetics.

Introduction – The original conclusion is missing "a" (before cosmetic ingredient) and an "s" for the word "concentration".

Acute, Inhalation – The 4-hour study in Sprague-Dawley rats (0, 38, 89 or 588 mg/m^3) cited to the ECHA dossier (reference 6) appears to be the same study that was cited to EPA and Collins et al. (1986) (an unpublished report) in the 2003 re-review (reference 5). Although the ECHA dossier does not provide details about the reference, they do provide a date, 1986. In addition to the matching rat strain, and exposure concentrations in the two descriptions, the particle sizes are stated as "1.3-6.7 µm" in the summary from the re-review, while the ECHA dossier gives the particle sizes as 1.31, 1.99 and 6.66 µm for the three exposure concentrations (low to high). If two descriptions of this study are left in the CIR report, the particle sizes should be added to the second description, and it should state that the ECHA dossier appears to be another source of the study that was included in the 2003 re-review.

Genotoxicity; Summary – The summary sentence: "Several gene mutation assays were performed, and the results were mixed." is misleading and is not necessary in the Genotoxicity section. In the Summary, it would be better to give a few details, e.g., Two Ames assays were

negative and a gene mutation assay in V79 cells was consistently positive without metabolic activation, but positive results were not reproducible with metabolic activation.

Clinical Studies – It would be helpful to state the country (or region) where the tertiary referral dermatitis clinic was located (reference 24).

Summary – In describing the inhalation study in Fischer rats, the duration of exposure (4 hours) should be stated.

Please include the range of time over which positive patch test outcomes decreased. Noting the timeframe will be especially helpful when this report is read years after it is published.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Priya Ferguson, M.S.
Associate Toxicologist/Senior Scientific Analyst/Writer, CIR

Date: September 25, 2026

Subject: Wave 2 - Safety Assessment of Alkyl Gallates

Comments on the Draft Final Amended Report have been received from the Council (*PCPCcomments_AlkylGallates_Wave2_102026*). The majority of these comments are editorial and will be addressed prior to posting the report.

Personal Care Products Council

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Jaap Venema, Ph.D.
EVP and Chief Scientist – Personal Care Products Council
Industry Liaison to the CIR Expert Panel

DATE: September 18, 2026

SUBJECT: Draft Final Amended Report: Amended Safety Assessment of Alkyl Gallates as Used in Cosmetics (October 2026 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft final amended report, Amended Safety Assessment of Alkyl Gallates as Used in Cosmetics.

Toxicokinetics; Summary – In the description of the PBK model, it would be helpful to note the modeled exposure dose, and if the predicted peak plasma concentrations were in rats or humans.

Developmental and Reproductive Toxicity – What was the frequency of dosing, e.g., /day, in the study of mice treated by intraperitoneal injection for 4 weeks (reference 31)?

Carcinogenicity, old report summary – Units of ppm (in the diet) should be called concentrations rather than doses.

Mutagenesis Enhancement, Copper-Dependent DNA Damage, Anti-Mutagenic Activity – It would be helpful if these sections were moved after the Genotoxicity section.

Cytotoxicity – Units of µM should be called "concentration" rather than "dose".

Effect on Hepatotoxicity, old report summary – In the intraperitoneal study, what was the dose of Caprylyl Gallate that was used with 50 mg/kg Propyl Gallate?

Estrogenic Effects – It would be helpful if this section was moved after the DART section.

Discussion – Rather than saying: "most of these ingredients are approved by the US FDA for use as antioxidants/preservatives in food", it would be clearer to state that "all but Ethylhexyl Gallate are approved by the US FDA for use as antioxidants/preservatives in certain types of food".

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COSMETIC
INGREDIENT REVIEW
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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Priya Ferguson, M.S.
Associate Toxicologist/Senior Scientific Analyst/Writer, CIR

Date: September 25, 2026

Subject: Wave 2 - Safety Assessment of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide

The Nail Manufacturer Council on Safety (NMC) provided an update regarding efforts to identify additional information relevant to the Panel's review of the phosphine oxide photoinitiators (*data1_PhosphineOxides_Wave2_102026*). NMC reported that its outreach to industry stakeholders did not identify additional data responsive to the Panel's requests and requested clarification regarding any specific information that the Panel considers a priority. In addition, updated concentration of use information on Ethyl Trimethylbenzoyl Phenylphosphinate and Bis-Trimethylbenzoyl Phenylphosphine Oxide were received (*data2_PhosphineOxides_Wave2_102026*). The maximum reported concentration of use for this ingredient group remains unchanged at 6.2% in nail polish and enamel for Ethyl Trimethylbenzoyl Phenylphosphinate. However, Bis-Trimethylbenzoyl Phenylphosphine Oxide is now reported to be used in nail polish an enamel at 0.69%; previously, no concentration of use had been reported for this ingredient.

September 14, 2026

Dr. Bart Heldreth
Executive Director
Cosmetic Ingredient Review
555 13th Street NW, Suite 300W
Washington, DC 20004

Re: Phosphine Oxide Photoinitiators – Nail Manufacturer Council on Safety Update

Dear Dr. Heldreth:

On behalf of the Nail Manufacturer Council on Safety (NMC), I am writing to provide an update regarding the Cosmetic Ingredient Review's (CIR) ongoing review of three phosphine oxide photoinitiators used in professional nail products:

Bis-trimethylbenzoyl phenyl phosphine oxide (BAPO, CAS #162881-26-7)
Ethyl trimethylbenzoyl phenyl phosphinate (TPO-L, CAS #84434-11-7)
Trimethylbenzoyl diphenyl phosphine oxide (TPO, CAS #75980-60-8)

Following the March 2026 Expert Panel meeting and CIR's determination that additional scientific information was needed to complete its safety assessments, NMC undertook an effort to identify potentially relevant information within the nail industry and among ingredient suppliers and manufacturers.

As part of that effort, NMC sought to engage with stakeholders including nail product manufacturers, ingredient and raw-material suppliers, formulators, and other industry participants. Our outreach specifically requested information potentially relevant to the Panel's questions, including dermal irritation and sensitization studies, phototoxicity or photoallergy data, toxicological studies or summaries, exposure and use information, photolytic decomposition and cured-system information, published or unpublished scientific literature, analytical data, impurity profiles, and manufacturing information, where appropriate.

While we had hoped that the broader industry outreach would identify additional data, the absence of additional information is itself useful information as the review proceeds. NMC believes it is important to communicate this outcome to CIR rather than duplicate efforts or pursue data generation that may not be responsive to the Panel's specific needs.

NMC would welcome clarification regarding whether CIR has identified specific studies, endpoints, or categories of information that it considers a priority at this stage. Continued guidance would help the

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industry determine whether meaningful additional information exists that has not yet been identified and avoid unnecessary duplication of effort.

Despite this outreach effort, NMC was unable to identify any additional data or information responsive to the Panel's requests including no additional dermal irritation or sensitization data beyond what has already been submitted to CIR. This outcome may simply reflect that no further data currently exists. NMC remains committed to supporting CIR's review and will promptly forward any relevant information that becomes available.

Thank you for your continued attention to this matter. Please do not hesitate to contact Myra Reddy at myra.probeauty.org with any questions.

Sincerely,
Leslie Perry, CEO
Professional Beauty Association (PBA)
Nail Manufacturer Council on Safety (NMC)

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Concentration of Use by FDA Product Category[1]

Ethyl Trimethylbenzoyl Phenylphosphinate
Bis-Trimethylbenzoyl Phenylphosphine Oxide

Ingredient	Product Category	Maximum Concentration of Use
Ethyl Trimethylbenzoyl Phenyl Phosphinate	Basecoats and undercoats	2.2%
Ethyl Trimethylbenzoyl Phenyl Phosphinate	Nail polish and enamel	4-6.2%
Ethyl Trimethylbenzoyl Phenyl Phosphinate	Other manicuring preparation	0.25-4.7%
Bis-Trimethylbenzoyl Phenylphosphine Oxide	Nail polish and enamel	0.69%

Information collected in 2025

Table prepared: June 25, 2025

Updated July 27, 2026: for Ethyl Trimethylbenzyol Phenyl Phosphinate: Added basecoats and undercoats; added 4.7% as maximum concentration for other manicuring preparations; added Bis-Trimethylbenzoly Phenylphosphine Oxide use in nail polish and enamel

[1] The new FDA cosmetic product categories under MoCRA were used for this survey.

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR
Jinqiu Zhu, Ph.D., Toxicologist, CIR
Date: September 25, 2026
Subject: Wave 2 – Amended Safety Assessment of Dibutyl Phthalate, Diethyl Phthalate, and Dimethyl Phthalate as Used in Cosmetics

Attached are comments dated September 24, 2026, from Weaving Voices for Health & Justice (WVHJ) on the Draft Tentative Amended Safety Assessment of Dibutyl Phthalate, Diethyl Phthalate, and Dimethyl Phthalate as Used in Cosmetics (identified as *WVHJcomments_Phthalates_Wave2_102026*).

In their comments, WVHJ raised three concerns. First, they urged the Panel to conclude that Dibutyl Phthalate is not safe as used in cosmetics and expressed concern regarding potential cosmetic exposure since the previous review. Second, they stated that the respiratory exposure language is not consistent with the Panel's respiratory exposure resource document because the RLD lists a deodorant spray product containing Diethyl Phthalate. They requested that the report state that 50% of particles from this product are likely to be respirable and that the respiratory implications be addressed in the Conclusion. Third, they requested inclusion of five studies reporting associations between personal care product use and urinary phthalate metabolite levels.

Response to WVHJ Comments

1. Requested Conclusion for Dibutyl Phthalate
WVHJ urged the Panel to conclude that Dibutyl Phthalate is not safe as used in cosmetics. The introductory statement primarily reflects WVHJ's position regarding the historical review and use of Dibutyl Phthalate; however, it does not present new scientific data demonstrating adverse effects attributable to cosmetic use during that period.

The Panel will determine the appropriate conclusion for Dibutyl Phthalate in accordance with CIR procedures, based on the totality of the available toxicological data, current practices of use and concentration, exposure information, and the resulting risk characterization.

2. Respiratory Exposure Language
Related respiratory exposure concerns were addressed in CIR's March 2026 response to WVHJ (see PDF page 14 -15, at https://www.cir-safety.org/sites/default/files/DataSupplement_Wave2_March2026.pdf). That response summarized the Panel's ongoing consideration of revised respiratory exposure boilerplate language and distinguished typical pump sprays from propellant-based sprays. Specifically, it noted that typical pump sprays generally produce only a small respirable fraction, whereas propellant-based sprays, including aerosol deodorant sprays and dry shampoos, may emit larger fractions of droplets or particles with aerodynamic equivalent diameters of less than 10 µm. It also noted that the proportion of respirable material depends on product characteristics and formulation and that deposition and potential effects in both the upper airways and deep lung should be considered.

For a spray product, the bulk particle size of the ingredient and the particle size of the formulation while it remains inside the container are not sufficient or directly informative for inhalation risk assessment. A meaningful product-specific inhalation exposure assessment instead requires characterization of the emitted formulation under conditions of use, including its airborne particle or droplet size distribution and concentration in the user's breathing zone, or, when available, the fraction or dose deposited in the respiratory tract, particularly the deep lung.[1] Accordingly, generic particle size data from other tested deodorant aerosols cannot establish that exactly 50% of the material emitted from the Diethyl Phthalate-containing product would be respirable or would reach the deep lung. Respiratory deposition also depends on the complete aerodynamic size distribution, airborne concentration, formulation, propellant, valve and nozzle design, manner of use, and breathing pattern. When an appropriate inhalation no-observed-adverse-effect concentration (NOAEC) and adequate product-

specific aerosol characterization and exposure data are available, inhalation risk may be evaluated using an estimated lung-deposited dose and a corresponding Margin of Exposure.

The Panel may determine whether the available data adequately support the reported spray use and whether the Discussion or Conclusion should include an additional qualification or data need for the particle size distribution and airborne concentration of the emitted aerosol in the breathing zone, the lung-deposited fraction, product-use patterns, and inhalation toxicity information.

3. Personal Care Product Use and Urinary Phthalate Metabolites

The five publications cited in the current comments were also identified in WVHJ's February 2026 comments and addressed in the March 2026 Wave 2 response memorandum. These studies are relevant to exposure context. Collectively, they report that use of personal care products, particularly fragrance-containing products, is associated most consistently with higher urinary monoethyl phthalate (MEP), the primary metabolite of Diethyl Phthalate, and less consistently with urinary monobutyl phthalate (MBP), a metabolite of Dibutyl Phthalate.

In the Health and Environmental Research on Makeup of Salinas Adolescents (HERMOSA) study, girls who reported daily makeup use had higher urinary MEP concentrations than girls who rarely or never used makeup (102.2 vs. 52.4 ng/ml, $p = 0.04$), and recent use of foundation, blush, or mascara was associated with higher MEP and MBP concentrations.[2] In adult men, use of cologne or aftershave within the previous 48 h was associated with higher median urinary MEP concentrations, and each additional type of personal care product used was associated with a 33% (95% CI: 14 - 53%) increase in MEP.[3] Studies in Mexican children and women also identified selected personal care products as predictors of urinary phthalate metabolites.[4,5] A more recent study reported the strongest associations between MEP and perfumes or other fragrance-containing products, including shampoos, body lotions, and hair products.[6]

These findings are consistent with personal care product use contributing to aggregate phthalate exposure, particularly Diethyl Phthalate-related exposure as reflected by urinary MEP. However, the studies generally relied on self-reported product use, and the presence and concentrations of individual phthalates in the products used were generally not analytically confirmed. In addition, urinary metabolites reflect recent aggregate exposure from both cosmetic and non-cosmetic sources. Consequently, the findings cannot be used to quantify exposure from a specific cosmetic formulation or to directly inform the margin of exposure calculations in this assessment. Because these studies evaluate associations between product use patterns and biomarkers of exposure rather than adverse health outcomes, they provide relevant exposure-context information but do not directly inform the toxicological safety determination for Diethyl Phthalate or Dibutyl Phthalate as used in cosmetics.

The Panel is asked to review WVHJ's comments and provide guidance on the proposed revisions to the respiratory exposure language and on whether the personal care product biomonitoring studies should be included in the report.

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WeavingVoices
FOR HEALTH & JUSTICE

September 24, 2026

Re: Comments on the Amended Safety Assessment of Dibutyl Phthalate, Diethyl Phthalate, and Dimethyl Phthalate as Used in Cosmetics

To the CIR:

The following comments are submitted on behalf of Weaving Voices for Health & Justice.

After 24 years of submitting comments on the health hazards of phthalates (our first Executive Director attended the CIR's 2002 meeting on phthalates in person) we are hopeful that the Expert Panel will conclude that dibutyl phthalate is not an ingredient that is safe as used in cosmetics. While we regret that two decades of potentially harmful exposure to this toxic chemical through the use of cosmetics could have been avoided with a more proactive CIR decision back in 2002, we are hopeful for cosmetics users going forward, that toxic chemical burdens are lessened by your current deliberations and conclusions.

Regarding the use of the other types of phthalates in cosmetics we would like to reiterate the following points which have not yet been addressed by the CIR.

1) **Language used in the Cosmetics use section regarding potential inhalation of products (p.71 of the .pdf) is not supported by the Panel's respiratory exposure resource document as claimed and should be corrected to be protective of health.**

   - The latest RLD data for diethyl phthalate clearly list a deodorant spray product containing this ingredient.
   - The CIR's inhalation resource document clearly reports the data that "*tested deodorant spray aerosols have a **median** d ae of 10 µm with a coefficient of variation of 0.3, suggesting that approximately **half** of these particles are within the range considered to be respirable*."
   - It is simply not accurate (nor protective of health) for the safety assessment to state:

     > "..the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount." (p.112 of the pdf

     The inhalation data the CIR relies on clearly show that **half** of the droplets/particles from deodorant sprays are small enough to be respirable deeply into the lungs, which wholly contradicts the claim that "*the majority of droplets/particles would not be respirable*".
   - The safety assessment should clarify that 50% of the particles from the deodorant spray containing diethyl phthalate are likely to be respirable (i.e. they **would** enter the lungs).

The respiratory health ramifications of this information should be discussed by the Expert Panel and included in the Conclusion.

2) **The Epidemiological Studies section (beginning on p. 80 of the .pdf) should include a discussion of the extensive data showing that personal care product use alone significantly increases the levels of phthalates found in the body.**

The Epidemiological Studies section is very clear that higher urinary concentrations of DEP and/or DBP are often correlated with higher risk of disease. The studies (and discussion) that are missing are any of the highly relevant studies showing the extent to which use of personal care products may be responsible for those higher urinary concentrations. The studies below show that cosmetic use alone significantly impact levels of phthalate exposure measured in the body – in some cases doubling or even tripling urinary concentrations.

- Examples include:

https://pmc.ncbi.nlm.nih.gov/articles/PMC6037613/ **Personal care product use as a predictor of urinary concentrations of certain phthalates, parabens, and phenols in the HERMOSA study**

"*Girls who reported using makeup every day vs. rarely/never had higher urinary concentrations of monoethyl phthalate (MEP) (102.2 ng/mL vs 52.4 ng/mL)… Girls who reported recent use of specific makeup products, including foundation, blush, and mascara, had higher urinary concentrations of MEP, mono-n-butyl phthalate (MBP)*."

https://pubmed.ncbi.nlm.nih.gov/16263507/ **Personal care product use predicts urinary concentrations of some phthalate monoesters**

Men who used cologne or aftershave within 48 hr before urine collection had higher median levels of monoethyl phthalate (MEP) (265 and 266 ng/mL, respectively) than those who did not use cologne or aftershave (108 and 133 ng/mL, respectively). For each additional type of product used, MEP increased 33% (95% confidence interval, 14-53%).

https://pubmed.ncbi.nlm.nih.gov/24041567 **Predictors of urinary bisphenol A and phthalate metabolite concentrations in Mexican children**

"We demonstrated that personal care product use is associated with exposure to multiple phthalates in children. Due to rapid development, children may be susceptible to impacts from exposure to endocrine disrupting chemicals; thus, reduced or delayed use of certain personal care products among children may be warranted."

https://pubmed.ncbi.nlm.nih.gov/35358548/ **Exposure to phthalates from personal care products: Urinary levels and predictors of exposure**

"The most striking association between any phthalate and PCPs was observed between MEP and perfumes or fragrance-containing products such as shampoos, body lotions and hair products."

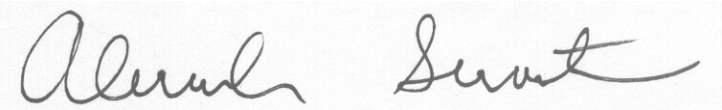
https://pubmed.ncbi.nlm.nih.gov/21429583/ **Personal care product use and urinary levels of phthalate metabolites in Mexican women**

"Our results suggest that the use of some personal care products contributes to phthalate body burden that deserves attention due to its potential health impact.

Admittedly, these types of epidemiological studies, (i.e. directly assessing impact on body burden from cosmetic product use) are relatively rare for most cosmetic ingredients, but as shown above, multiple studies do exist for phthalates. These studies showing cosmetic use as a demonstrated predictor of elevated urinary levels of phthalate metabolites is clearly highly relevant information to include in a cosmetic ingredient safety assessment. The CIR Expert panel should be concerned that the omission of this well-known important information may appear to readers as intentional.

Thank you for your consideration of these comments.

Sincerely,



Alexandra Scranton

Director of Science and Research

Weaving Voices for Health & Justice

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Temima Nguyen, M.S., Scientific Analyst/Writer, CIR
Date: September 25, 2026
Subject: Wave 2 - Safety Assessment of Polyacrylate-13 as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Report on Polyacylate-13 *(PCPCcomments_Polyacrylate-13_Wave2_102026).* The comments are primarily editorial in nature and will be addressed following the October Panel meeting.

Personal Care Products Council

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Jaap Venema, Ph.D.
EVP and Chief Scientist – Personal Care Products Council
Industry Liaison to the CIR Expert Panel

DATE: September 18, 2026

SUBJECT: Draft Final Report: Safety Assessment of Polyacrylate-13 as Used in Cosmetics (October 2026 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of Polyacrylate-13 as Used in Cosmetics.

Cosmetic Use – In the first sentence of the new baby products paragraph, it would be helpful to use the specific product category, baby lotions/oils/powders and creams, rather than the general category baby products.

Discussion – In the paragraph on residual acrylamide levels, it would be helpful to note that the supplier indicated a residual acrylamide concentration of <1 ppm in the trade name mixture in which Polyacrylate-13 is sold.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Priya Ferguson, M.S.
Associate Toxicologist/Senior Scientific Analyst/Writer, CIR

Date: September 25, 2026

Subject: Wave 2 - Safety Assessment of Prostaglandin Analogues

Comments on the Draft Tentative Report have been received from EAS Consulting Group, LLC (*comments_ProstaglandinAnalogues_Wave2_102026*). These comments suggest that the Draft Tentative Report be revised to accurately reflect the SCCS conclusion for Ethyl Tafluprostamide and Isopropyl Cloprostenate, stating "cannot be considered safe," rather than "are not considered safe," emphasizing that the SCCS conclusion was based on identified data gaps rather than demonstrated adverse effects.

TO: Bart Heldreth, PhD, Executive Director
Cosmetic Ingredient Review
Washington, DC
heldrethb@cir-safety.org

FROM: Jay Ansell, PhD, DABT, ERT
John Bailey, PhD
EAS Consulting Group, LLC
Jay.Ansell@easconsultinggroup.com
On behalf of the 0.005% IC Sponsor and the DDDE Sponsor

DATE: September 22, 2026

RE: Wave 2 Submission - Safety Assessment of Ethyl Tafluprostamide and Isopropyl Cloprostenate as Used in Cosmetics

We respectfully submit the following comments on the *Draft Tentative Report for Panel Review of the Safety Assessment of Ethyl Tafluprostamide and Isopropyl Cloprostenate as Used in Cosmetics, dated September 11, 2026*.

We write to point out an inconsistency in the October 2026 report package and to request a conforming correction. The meeting agenda transmittal memorandum accurately reports the SCCS conclusion: the ingredients, at the stated concentrations, *cannot be considered safe*. The USE section of the Draft Tentative Report inaccurately states that the SCCS concluded that the ingredients, at the stated concentrations, *are not considered safe*. The two phrasings are not interchangeable.

SCCS's "*cannot be considered safe*" conclusion indicates that the SCCS was unable to establish, on the basis of the scientific information assessed, conditions of use under which the ingredients could be considered safe in cosmetic products. While we disagree with the SCCS's conclusion, the Opinion rests on the absence of data, not on demonstrated harm: not having accepted the applicants' read-across, the SCCS grounded its conclusion on pharmacological potency together with the lack of acceptable data that would permit reproductive and developmental effects to be excluded. Were the European Commission ultimately to prohibit these ingredients under Annex II, that measure would be a separate regulatory response under "the precautionary principle" to the data gap, not a scientific finding that the ingredients are unsafe.

The CIR Panel operates under a different framework. Under Section 42 of the Procedures, the Panel evaluates "whether each ingredient, under each relevant condition of use, is safe, or is not safe, or there are insufficient data or information to make a determination that the ingredient is safe under its intended conditions of use." Each of these conclusions carries a distinct meaning within the CIR framework, and the distinction between a finding that rests on affirmative evidence of harm and one that reflects unresolved data gaps is one the Panel's own procedures preserve. The sponsors raise the SCCS phrasing point so that the record before the Panel accurately reflects the basis for the SCCS Opinion – a basis grounded in identified data gaps rather than demonstrated

adverse effects – and so that the Panel's characterization of the SCCS Opinion aligns with the conclusion the SCCS itself expressed.

Accordingly, the sponsors respectfully request that the Panel conform the USE section phrasing of "*are not considered safe"* to the SCCS Opinion and memorandum phrasing of "*cannot be considered safe*."

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, MSES, Senior Scientific Analyst/Writer, CIR
Date: September 25, 2026
Subject: Wave 2 – Amended Safety Assessment of Pyrogallol as Used in Cosmetics

Please find attached the comments provided by the Personal Care Products Council on the Draft Final Amended Report on Pyrogallol. The comments are largely editorial in nature; however, the Panel should review the comment regarding wording in the Discussion and determine if changes should be made.

Personal Care Products Council

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Jaap Venema, Ph.D.
EVP and Chief Scientist – Personal Care Products Council
Industry Liaison to the CIR Expert Panel

DATE: September 18, 2026

SUBJECT: Draft Final Amended Report: Amended Safety Assessment of Pyrogallol as Used in Cosmetics (October 2026 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft final amended report, Amended Safety Assessment of Pyrogallol as Used in Cosmetics.

Key Issue

The Discussion is confusing. It says: "The Panel noted a lack of relevant safety data, especially data that pertain to new product category uses outside of hair dyes, and determined that the data needs from the Insufficient Data Announcement issued following the June 2025 Panel meeting remain unmet." Yet, the data needs do not specifically ask for anything about use in product categories that are not hair dyes (like concentration of use for the other categories). The Discussion also notes that based on the FD&C Act, Pyrogallol should not be used in products other than hair dyes.

If it is the intent of the Expert Panel to review only the safety of this ingredient when used in hair dye products and to leave the other products to FDA to regulate, this should be more clearly stated in the Discussion.

Additional Considerations

Cosmetic Use; Summary – It would be helpful to note that there were no use concentrations reported in a CTFA survey conducted for the 2007 re-review.

Cosmetic Use – Please correct: "Pyrogallol is not approved color additives" (add "an" before approved, and delete "s" in additives)

Genotoxicity; Table 3 – Based on the text, it is not clear how the results in the chromosomal aberration test differed by pH (reference 22). The text states: "at pH 6.0, a significant increase in chromosomal aberrations was observed at 60 and 80 µM and at pH 7.4 and 8.0, significant chromosomal aberrations were induced at <80 µM." The text does not indicate how many concentrations less than 80 µM were tested. Table 3 indicates that the lowest concentration tested was 20 µM, but it is not clear from the Table if significant chromosomal aberrations were induced at all test concentrations as it also just says "<80 µM".

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