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PERSPECTIVE

A Perspective on the Safety of Cosmetic Products: A Position Paper of The American Council on Science and Health

Gilbert Ross, editor
The American Council on Science and Health, New York, New York, USA

Over the years, some activist groups have targeted cosmetics as possible human health threats, claiming that cosmetic ingredients are not adequately tested for safety and may pose risks to consumers. The groups allege that industry practices related to safety testing are flawed, that there is little government oversight, and that cosmetics contain cancer-causing chemicals and other toxicants. A critical review of the scientific data related to these claims indicates the following: (1) Industry has the primary responsibility to ensure that all ingredients, preservatives, and coformulants used in products are safe for their intended uses. (2) The U.S. Food and Drug Administration (FDA) has regulatory oversight of the cosmetic industry. Its authority includes the banning or restriction of ingredients for safety reasons. (3) The Cosmetic Ingredient Review (CIR), an independent, scientific review board, critically evaluates chemical ingredients used in cosmetics and publishes the results of its findings in the peer-reviewed literature. (4) Health-related allegations about cosmetic ingredients are generally based on the results of high-dose laboratory testing in animals and have little relevance for humans. As true now as when Paracelsus said it in the 16th century, "It is the dose that makes the poison." (5) The health-related allegations involving specific chemicals (e.g., phthalates, parabens, and 1,3-butadiene) fail to consider important scientific studies and recent regulatory conclusions about these chemicals, which have found that they are not hazardous. (6) Animal and human physiology differ in crucial ways, further invalidating simplistic attempts to extrapolate rodent testing to human health risks. The cosmetic industry should be encouraged to publish more of its toxicity studies and safety evaluations, which would aid in dispelling the uncertainty that some consumers have about cosmetic safety.

Keywords 1,3-Butadiene, Carcinogen, Cosmetics, Parabens, Phthalates

Cosmetics, such as lipstick, hand lotion, eyeliner, toothpaste, blush, and antiperspirant, are products that millions of us use daily. Recently, numerous claims, largely from activist groups, contend that cosmetic products, in general, are not regulated stringently enough and contain ingredients that pose risks to human health. These serious claims call for an evaluation of the data, toxicological principles, and current safety evaluation approaches (ones that evaluate both hazard and exposure).

In its review of the information relevant to these claims, the American Council on Science and Health (ACSH) has included an examination of:

- industry practices and stewardship related to safety testing and evaluation of ingredients;
- regulation of such products by the Federal government,
- history of use and testing of some specific cosmetic ingredients.

In doing so, we will discuss the key principles of dose-response and the actual exposure of humans from the use of cosmetic products, as well as the limitations of extrapolating high-dose laboratory animal results to humans.

REGULATION AND SAFETY EVALUATION OF COSMETICS

The Role of Industry in Safety Evaluation and Testing

Although the U.S. Food and Drug Administration (FDA) has a key role in the regulation and management of cosmetics in commerce, guided by scientific input provided by an independent science review board (the Cosmetic Ingredient Review or CIR), it is the cosmetic industry that is responsible for insuring

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Address correspondence to Gilbert Ross, MD, Executive and Medical Director, The American Council on Science and Health, 1995 Broadway, New York, NY 10023, USA. E-mail: rossg@acsh.org

the safety of its formulations and products for consumers. Safety testing is an essential requirement if a company expects to conduct business in the U.S. without the burden of product recalls, consumer complaints, and lawsuits over alleged injury. As a part of product stewardship, companies are obliged to ensure the safety of their products and ingredients for use as specified on the product label. Cosmetic companies typically strive to accomplish this through several mechanisms, including (a) industry standards for good manufacturing practice, (b) use of ingredients that have undergone safety testing and whose inclusion in cosmetic formulations for decades without evidence of adverse effects has demonstrated their safe use, (c) worldwide regulatory standards, and (d) continued evaluation and testing of currently used and new ingredients.

Cosmetic companies typically approach safety evaluation by focusing on the route and duration of potential exposure, as well as the chemical structures of ingredients, as key components that drive subsequent activities in the process. For example, experiments in laboratory animals using the oral route of exposure are of less relevance than studies employing dermal applications and exposures. Similarly, relative to duration of exposure, concerns about a shampoo that might inadvertently splash into the eye do need to be evaluated using laboratory animals that are continually exposed to that product (or ingredient) for hours per day and often for multiple days. The safety evaluation process, coupled with elements of risk assessment, includes the following steps:

Hazard Identification and Information Review: The first step involved in safety evaluation is a thorough review of the existing information for a proposed new ingredient. Sources could include public databases, toxicological reviews, testing information from suppliers of the ingredient, results from previously conducted testing, structure-activity analysis to obtain insight from similar materials for which extensive data already exists, and information about the metabolic/kinetic profile of the substance (absorption, distribution, excretion, and metabolism). Once the available information is assessed, recommendations are made including the identification of data gaps relative to testing in order to ensure that all toxicological endpoints and/or concerns have been addressed.

Exposure Assessment: Characterization of potential human exposure is conducted in order to understand the levels, routes, and durations of exposure that are relevant for consumers. The exposures that humans would likely encounter can be estimated from the anticipated use patterns, along with information on dermal absorption in animal models. Total exposure estimates need to include sources other than cosmetics, such as food, water, and inhalation, when applicable to individual substances (e.g., parabens in food).

Safety Testing: Because of the large historical database that the cosmetic industry has acquired over the years, there is a significant amount of information on the effects and toxicological profiles of many commonly used ingredients. As a result, the industry can often use existing information or employ in vitro and alternative methods when new information is required. If testing is deemed necessary to fill a critical data gap, then appropriate animal, human, or in vitro (nonanimal) models can be used. Dermal irritation, dermal sensitization, and the ability of an ingredient or product to move through the skin (transdermal penetration) are key data needs for many products, and it is incumbent on companies to procure this information. Numerous studies, perspectives, and methodologies have been published in the peer-reviewed literature detailing approaches that are used in the safety evaluation process. Dermal studies are particularly helpful since the skin is the primary route of exposure to humans from most cosmetics, toiletries, and fragrances (Gerberick, Robinson, and Stotts 1993; Gerberick and Robinson 2000; Robinson et al. 1989).

In addition to the evaluation of potential dermal effects, information on acute oral toxicity is important because of possible accidental ingestion by a child or adult. To address questions about long-term exposure and potential systemic effects, a number of end points of toxicity are considered during the safety evaluation process. These include effects on the major systems of the body such as reproductive and developmental toxicity, respiratory toxicity, and carcinogenicity. Ocular irritation is also important and the use of in vitro techniques to obtain this information is quite common. It is incumbent on the cosmetic industry to ascertain accurate and appropriate information for all relevant end points, whether that be through existing studies, documentation of safe use with no evidence of safety concerns, structure-activity modeling or extrapolation of data from similarly structured compounds, or actual testing, in order to address questions about an ingredient's potential to elicit acute or chronic effects.

Through hazard identification (i.e., addressing all critical toxicological end points) and exposure assessment, a risk characterization can be developed to determine whether an ingredient is safe for use without foreseeable adverse effects or toxicity. This determination typically includes an adequate margin of safety to protect against unexpected toxicity or adverse effects if the product is misused or abused, counter to any recommended use on the product label. Although of theoretical concern, there is no evidence that the aggregate exposures to the chemicals discussed herein lead to additive potential toxicity as compared to each individual exposure.

The Role of the Food and Drug Administration

The U.S. FDA Center for Food Safety and Applied Nutrition (CFSAN) is the primary arm of the federal government charged with oversight for programs and policy related to multiple aspects of cosmetic use and safety. The FDA has authority over (a) cosmetic products and ingredients; (b) labeling requirements and label claims, which serve as key sources of information for consumers; (c) specific guidance on recall policies; and (d) bans on ingredients. Although it is not our purpose to cover all aspects

of FDA authority over the cosmetic industry, it is important to understand the breadth of its authority and that cosmetics in the marketplace are not operating in a vacuum without oversight relative to safety. Specifically, the FDA has the authority to:

- ban or restrict ingredients due to safety concerns,
- work with manufacturers to implement nationwide product recalls,
- mandate warning labels on products,
- inspect facilities that manufacture cosmetics,
- issue warning letters,
- seize illegal products,
- prosecute violators.

The Federal Food, Drug, and Cosmetic Act (FD&C) is an important law pertaining to cosmetic products marketed in the United States. It prohibits marketing of adulterated or misbranded cosmetic products and also tracks violations involving cosmetic ingredients, contaminants, processing, packaging, or shipping and handling. Federal law states that a cosmetic can be deemed to be adulterated if "it bears or contains any poisonous or deleterious substance, which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under conditions of use as are customary and usual [with an exception made for hair dyes]" (FDA 2005). This statement places the burden of safety directly upon the cosmetic industry, and it is incumbent upon industry members to ensure safety to consumers.

The Federal government does not subject cosmetics to premarket approval or require specific regulatory testing, such as that required for agricultural chemicals and pharmaceutical products. However, if a company fails to certify that adequate testing and evaluation have been conducted to substantiate the safety of a cosmetic product or its ingredients prior to marketing, the product must conspicuously have on its label: "Warning—The safety of this product has not been determined" (FDA 2005; 21 CFR 740.10). (In practice, such labels are generally only found on a product that has been challenged after it appeared on the market.) Conversely, the absence of this statement on a product label indicates that a company has evaluated the cosmetic product and certifies its safety for use as directed on the product label.

The FDA also has the ability to request a product recall or to recommend that a company order a recall for any number of reasons, consumer safety being among the most compelling. As an example, in March of 2005, Rose Art Industries voluntarily recalled certain face painting products after receiving consumer complaints that children had experienced minor adverse reactions from multiple colors of face paints (www.fda.gov, March 24, 2005). The complaints were described chiefly as dermal reactions—irritation, rash, itching—and typically lasted no more than a few days. In this particular case, the company took action to ensure that no additional children would suffer adverse or negative reactions to its products.

There are chemical ingredients that the FDA has determined, due to concerns about consumer safety, should not be used in cosmetic products. Such restricted ingredients include bithionol, which was restricted from use over 35 years ago (due to photosensitization potential); mercury (neurotoxicity concerns); vinyl chloride (because of central nervous system effects and carcinogenicity concerns); certain halogenated salicylanilides used as antimicrobial agents (owing to dermal effects including photosensitization); zirconium-containing complexes (due to respiratory concerns); chloroform (because of liver tumors in rodents following lifetime oral ingestion); and methylene chloride (because of tumorigenicity in laboratory animals following lifetime inhalation exposure) (21 CFR, Vol. 17, 2002). Additionally, color additives must be tested for safety by cosmetic and/or color manufacturers and subsequently gain approval by the FDA for their intended use. Thus, it should be clear that the FDA has a vital and significant role in the overall safety evaluation and monitoring of cosmetic ingredients and products.

The Role of the Cosmetic Ingredient Review (CIR)

The U.S. FDA, the Consumer Federation of America, and the Cosmetic, Toiletry, and Fragrance Association (CTFA; which serves as the primary industry trade association) established the Cosmetic Ingredient Review (CIR) (www.cir-safety.org) in 1976. The CIR is an independent scientific body and, although it is funded by the CTFA, this organization has neither editorial nor voting control over CIR opinion. The voting members of the CIR expert panel include scientists who have been publicly nominated by consumer, scientific, and medical groups; government agencies; and industry. By thoroughly reviewing and assessing the safety of ingredients used in cosmetics in an open manner, and publishing those results in a peer-reviewed scientific journal, the CIR process provides an important mechanism for evaluating the ingredients of cosmetics to ensure the safety of consumers who use such products.

Through a prioritization process that considers the extent to which consumers may be exposed to a particular ingredient in a cosmetic product, along with potential biological activity, the CIR conducts extensive literature searches on the evaluation of ingredient safety. This includes (a) physical and chemical properties; (b) absorption, distribution, excretion, and metabolism; (c) in vitro data; and (d) animal toxicology test data including acute, short-term, subchronic, and chronic studies, as well as dermal irritation and sensitization endpoints. Additionally, any clinical data are assessed, including epidemiological studies along with available repeat insult patch (i.e., dermal) tests. If it is determined through this process that the scientific literature contains insufficient information, the Panel will make these deficiencies known publicly in the peer-reviewed scientific literature. After an open process that includes several opportunities for public comment, a final report on those ingredients that have undergone CIR review is published in the *International*

Journal of Toxicology, a publication of the American College of Toxicology.

Although the FDA has banned the use of specific chemicals in cosmetic products, as previously discussed, the CIR has also recommended to the cosmetic industry the restricted use, or limits in concentration, for hundreds of other ingredients. The CIR process and the safety assessment can result in one of four conclusions for a particular ingredient following evaluation (www.cir-safety.org):

1. safe in the practices of use and concentrations as described in the safety assessment,
2. safe with qualifications that should be heeded to assure safe use,
3. insufficient data to support safety,
4. unsafe for use in cosmetics.

It is important to note that in reviewing the history of the CIR database, three of the four categories include some restrictions regarding use (www.cir-safety.org). The CIR has reviewed over 1200 ingredients and has recommended restrictions for hundreds of ingredients. For those ingredients for which insufficient data exist and for those with qualifications around use, the CIR identifies data gaps or restrictions, providing a guideline and impetus for industry to develop the necessary data and recommendations for the safe use of a cosmetic ingredient, or to use their own currently existing data to fill in the gaps. If the industry and individual cosmetic companies would make the results of testing and evaluation more transparent, possibly through scientific publication, confusion about safety testing of cosmetics would likely be reduced.

A REVIEW OF ALLEGATIONS AGAINST COSMETIC INGREDIENTS

The Claims about Cosmetics

Because much of the concern over cosmetics has centered on specific chemicals or even classes of chemicals, it is relevant to review the science and data upon which those claims are based. Several groups have alleged that cosmetic ingredients pose a potential health hazard and risk to humans (EWG 2005; www.thinkbeforeyoupink.org; www.wen.org), although it is difficult to evaluate their claims, as scientific support and specific references are rarely provided. In addition, many claims are general in nature without specific reference as to their scientific basis.

For example, the Environmental Working Group (EWG) publication "Skin Deep" contains the following statements:

> *"Few individual ingredients pose excessive risks, but most people use many products in the course of a day, so it well may be that these risks are adding up."*
>
> ACSH COMMENT: This statement is speculative. While additivity (or synergism) relative to risk may be of more concern if chemicals target the same tissue or organ, there is no evidence that cosmetic ingredients at the levels used in cosmetics yield a harmful effect either singly or in combination. If it were shown that multiple chemicals used over the course of a day target the same tissue, or empirically increased the incidence of some well-characterized adverse endpoint, the issue of additivity might become more relevant.

Although the *Food Quality Protection Act* of 1996 expressed regulatory concern about additive pesticide toxicity, this is not a requirement applicable to cosmetics (nor, indeed, has additive toxicity been shown to be a factor relevant even to pesticides).

> "*Nearly 70 percent of all products contain ingredients that can be contaminated with impurities linked to cancer and other health problems.*"
>
> COMMENT: This statement most likely pertains to findings in high-dose laboratory animal experiments and not to evidence that is necessarily relevant to humans. Many of the claims against cosmetics—including the above-mentioned "impurities"—ignore the fact that (1) the *presence* of a certain chemical in a cosmetic product is often a fraction of what was tested in animals (e.g., 5% or less in product versus 100% tested in laboratory animals); (2) the actual *exposure* of humans is far less than that administered to laboratory animals (dermal penetration from cosmetic use results in much lower systemic doses than from oral administration in laboratory animal studies); (3) animal physiology and metabolism are often quite different from human processes, and (4) the *route of exposure* is different in that humans typically do not ingest cosmetics (e.g., oral exposure) as do test animals. One exception to this is lipstick, which the FDA considers an ingestible. As a result, the FDA requires a thorough examination of the safety of color additives, which in turn are subjected to toxicological evaluation and testing.

Another example is the statement on the website www.breastcanceroptions.org that "studies have shown that products containing paraben preservatives promote estrogenic activity to the same extent as human estrogen" (Coleman 2003). No citations or references are provided, and therefore it is difficult to determine the validity of this statement and answer many questions that arise. For example, which paraben preservatives are the subjects of this claim? Moreover, in what test system (in vitro, in vivo, whole animal) have they been shown to promote estrogenic activity? How do the levels of paraben in laboratory tests compare to (a) typical levels used in product and (b) the level and potency of natural estrogen in the human body? Although we know that in some laboratory systems, parabens have been shown to possess very low potency estrogenic activity, this activity is many orders of magnitude below natural human hormonal activity.

A last illustration is an article by the Cancer Prevention Coalition on the Web site www.ecomall.com, which states that "cosmetics are even more deserving of warning labels since the hazardous ingredients pose risks of cancer, genetic damage, and reproductive toxicity, including infertility to virtually the entire U.S. population of unsuspecting consumers, and their infants and children" (www.ecomall.com 2005). This is an incredibly broad and serious statement. It is not accompanied by any scientific data or references and appears to be aimed at garnering the

attention of consumers and spawning concern and fear, without providing critical details or context.

Evaluating the Claims Using the Risk Assessment Paradigm

Hazard Analysis

Many of the claims against cosmetics and their ingredients involve cancer, reproductive harm, and genetic damage, although the authors fail to acknowledge that there are no known data or studies linking cosmetic use to cancer, reproductive harm, or genetic damage in humans.

As previously discussed, the first step in safety evaluation is the development of the toxicological profile for a specific ingredient that involves identifying the sentinel hazards associated with a chemical. It is therefore perplexing that the EWG report focuses almost exclusively on cancer as a concern and not on other more realistic outcomes from cosmetic products that are used primarily on the skin (i.e., skin irritation, sensitization). There is no known association between cosmetic use and cancer in humans. It is noteworthy that a recent analysis that assessed the potential association between cancer (including breast cancer) and hair dye use found no strong evidence of increased risk to humans (Takkouche, Etminan, and Montes-Martinez 2005).

It is important to recognize that the majority of chemicals designated as possible human carcinogens are classified as such based almost exclusively on laboratory animal data. Moreover, most cancer classification systems are hazard based, which means they do not consider the amount of exposure (i.e., they rely on effects reported in high-dose animal studies) when evaluating human health risk. When references are made to chemicals as "possible or suggestive human carcinogens," it is imperative that the context behind those labels be provided—including animal species, dose, and route and duration of exposure (Meister 2005). For cosmetics, those ingredients that have been associated with oncogenic effects in laboratory animals are typically administered at doses far above anticipated human exposure levels using a route of exposure (oral) that may not be relevant for humans.

A recent report attempted to link breast cancer in humans to exposure to underarm deodorants containing aluminum salts (Darbre 2005), while the same author and cohorts found parabens in breast tumor tissue (Darbre et al. 2004), which caused them to express concern about a causal association. These studies are preliminary and represent more theoretical than cause-and-effect evidence of any real link.

Exposure Analysis

Virtually all claims that cosmetic ingredients may be unsafe are based on hazard alone and do not consider exposure, and hence, quantitative risk assessment. In addition to the amount of exposure, the route of exposure is critical as well. Cosmetics are not normally ingested, although this is the primary route of exposure used in toxicological testing. Cosmetics are primarily applied to the skin and skin structures (e.g., hair and nails), and therefore route to route extrapolation (oral ingestion in laboratory studies to dermal penetration in humans) cannot be assumed to approximate effects following dermal exposure because of differences in internal systemic dose (i.e., oral exposure is more likely to result in a higher internal dose than dermal exposure). In addition, the skin provides a barrier to significant penetration and systemic absorption. However, the EWG report does not discuss estimates of human exposure to cosmetic ingredients compared to those doses used in laboratory studies, and this comparison is necessary in order to determine how robust the margins of safety are between those levels that caused effects in animals compared to typical human exposure levels.

An analysis of the available data for 1,3-butadiene, which is alleged as an impurity of concern, demonstrates deficiencies in the EWG's approach. The EWG authors base their concern on mammary tumors in laboratory animals, whereas the National Toxicology Program (which the EWG report cites), considers carcinogenic potential for 1,3-butadiene to be based on lymphatic and/or hematopoetic neoplasms as the primary or most relevant sensitive endpoints on which cancer risk is assessed, neither of which are mentioned by the EWG (NTP 2005). In addition, there are epidemiological (i.e., human) studies of 1,3-butadiene exposure that the EWG fails to discuss. Finally, the Environmental Protection Agency (EPA) has based the reference concentration (permissible lifetime exposure concentration for humans) for 1,3-butadiene on reproductive toxicity in mice, which it considers the most sensitive endpoint for purposes of risk extrapolation to humans and includes a thousand-fold safety (uncertainty) factor in this derivation (IRIS 2002). This example reinforces the importance of first determining the most relevant target organ for purposes of risk assessment. In its report, the EWG fails to provide even a rudimentary risk assessment for any of the ingredients it claims pose health risks—one incorporating accurate hazard identification, dose-response analysis, exposure assessment, and the resultant characterization of risk.

SPECIFIC CONCERNS: PHTHALATES AND PARABENS

The specific allegations that have been made must be evaluated using available scientific data. For example, the group Breast Cancer Action claims that "phthalates are known to cause a broad range of birth defects and lifelong reproductive impairments in laboratory animals that are exposed to these chemicals during pregnancy and after birth. Phthalates are also known to be hormone-mimicking chemicals, many of which disrupt normal hormonal processes, raising concern about their implications for increased breast cancer risk" (www.thinkbeforeyoupink.org). How should a consumer interpret such a claim?

Similarly, the report "Skin Deep" notes that "dibutyl phthalate (DBP) is an industrial plasticizer and well-established reproductive toxin that targets the male reproductive system" (EWG 2005). In addition, the report makes the sweeping claim that "trends in human male reproductive health include, many of the

same effects seen in lab animals dosed with phthalates." In both cases, the authors of these reports fail to mention the concentrations, durations, and routes of exposures used in the studies, and the reader is left to assume that the hazards identified in laboratory studies are relevant to humans, which is a significant jump. This report therefore undertook a critical evaluation of the phthalate data, one of the most studied classes of chemical in recent years. The uses of dibutyl phthalate (DBP) and diethyl hexyl phthalate (DEHP) were considered.

Phthalates

Although phthalates are alleged to be associated with various health effects, we will focus on potential reproductive or developmental effects based on laboratory animal studies. There are no compelling data to suggest that human cancer, including breast cancer, is a relevant toxicological concern resulting from phthalate exposure. The International Agency for Research on Cancer (IARC) has concluded that rat tumor data and long-term (i.e., cancer) studies of DEHP in animals are of limited relevance to the evaluation of human risk, owing to differing mechanisms of toxicity between rats and humans. This conclusion resulted in a downgrade of DEHP's cancer classification to "not classifiable as to carcinogenicity in humans" (IARC 2000).

The report "Skin Deep" fails to include many of the reviews of phthalates that have been performed at the government and academic levels over the past 5 years. One of the sentinel reviews for seven different phthalates was published in 2000 by the Center for Evaluation of Risks to Human Reproduction (CERHR), an arm of the National Institutes of Health's National Toxicology Program (NTP). Among the chemicals evaluated were DBP and DEHP, both alleged to cause potential health risk to humans from cosmetic use.

Dibutyl Phthalate (DBP)

The CERHR review panel, which brought together recognized experts in fields germane to this analysis and those familiar with phthalate toxicology, concluded that it "has minimal concern about effects to human development and development of the reproductive system from current estimated exposure to DBP." The panel reviewed and assimilated the animal toxicology database along with estimates of human exposure and made an informed judgment on the possible risk to human health. Exposure was the key variable that enabled the panel to make these conclusions, but exposure was not addressed in the EWG report. The panel concluded that, "Dermal contact with products containing DBP is possible, but absorption through skin is most likely minimal" (CERHR 2000). Studies in rats have demonstrated that absorption of DBP through skin is fairly slow (Elsisi, Carter, and Sipes 1989). Further, an in vitro study conducted with rat and human skin has demonstrated that human skin is much less permeable to DBP than rat skin (Scott et al. 1987). These authors reported that the dermal absorption rate for DBP is very slow, on the order of 0.07 μg/cm^2/h, a rate that would provide negligible systemic exposure, even assuming contact with 100% DBP, which is not realistic for cosmetic products (Scott et al. 1987). Thus, once the concepts of dose, exposure, and relevance to humans are considered, assuming human risk based on lab studies of animals becomes much less plausible.

Diethylhexyl Phthalate (DEHP)

Diethylhexyl phthalate (DEHP) is another cosmetic ingredient phthalate that has been alleged to pose a potential health risk to humans. The following are some conclusions of various government and other groups regarding the risk to humans from exposure to DEHP and other phthalates:

- U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, March, 2005: "At the present time, FDA does not have compelling evidence that phthalates, as used in cosmetics, pose a safety risk. If FDA determines that a health hazard exists, the agency will advise the industry and the public and will consider its legal options under the authority of the Federal Food, Drug, and Cosmetic Act in protecting the health and welfare of consumers" (CFSAN 2005).
- Center for Evaluation of Risks to Human Reproduction (CERHR 2000; NTP 2005), the expert panel that evaluated seven different phthalates, noted: "The Panel has a minimal concern that ambient exposures adversely affect adult human reproduction. This level of concern is not appreciably altered for adults medically exposed to DEHP or MEHP (metabolite of DEHP)" (CERHR 2000). This latter statement is significant in that it implies that the Panel does not expect a greater risk for humans who receive greater exposures to DEHP as a result of unique exposures resulting from medical conditions (such as those undergoing dialysis or blood transfusions). For healthy infants, toddlers, and critically ill infants, the Panel expressed greater concern owing to the higher relative exposure and possible greater sensitivity of these age groups based on animal studies. However, it should be stressed that for these higher-risk humans, the dose and route of exposure (i.e., parenteral) are significantly different than those relevant to cosmetic use (i.e., lower concentrations and skin application which results in much lower systemic exposure).

As a result of the CERHR review, which identified data needs that would add to the toxicological database for DEHP, additional data have been developed over the past 5 years that improve our ability to evaluate the safety of DEHP for use in products. These new data include the following observations:

- New reproductive toxicity studies indicate that the oral no-observed-adverse-effect level (NOAEL) for DEHP (46 mg/kg bw/day) is about 10 times higher than the

NOAEL used by the Expert Panel in its first evaluation (3.7 to 14 mg/kg bw/day) (Wolfe et al. 2002).

- Biomonitoring data demonstrate that general population exposures are about 10 times lower than the estimate used by the Expert Panel in its initial deliberation (Blount et al. 2000; David 2000; Kohn et al. 2000).
- At the time of the Panel review, there were no multigeneration studies of DEHP in rodents. Since that time, four multigeneration studies of DEHP in rodents have been completed, none of which reported male reproductive effects or other adverse findings at dietary levels below 46 mg/kg bw/day, contrasted with the 3.7 to 14 mg/kg bw/day NOAEL range that was used by the Expert Panel during its review (Wolfe et al. 2002; Schilling, Gembhardt, and Hellwig 2001; Tanaka 2002, 2005).

Finally, and perhaps most significant for relevance to humans, a reproductive study in marmosets (monkeys) has been conducted, including the generation of pharmacokinetic data, which together provide support for the Panel's conclusion that "blood-MEHP levels associated with the ability of high-dose oral exposure to induce reproductive toxicity in rodents may never be achieved from oral exposure in most humans" (CERHR 2000; Kessler 2004). The significance of this last finding is that there is general scientific consensus that monkeys (primates) provide a more appropriate model than rats for evaluation of reproductive hazard to humans (the key end point of concern for many phthalates). Additionally, the marmoset monkey shows lower sensitivity to DEHP than rodents, as evidenced by the recent study in monkeys in which no adverse testicular toxicity was observed from weaning to adulthood at exposures up to 2500 mg/kg bw/day (Tomonari et al. 2003). Together, these recent data, none of which are cited or discussed by the EWG in their report, illustrate that there does not appear to be concern for risk to humans from anticipated daily exposures. It is noteworthy that the CERHR, FDA, and others do not even mention cosmetics or dermal exposure as a significant source. There is an extensive literature on phthalates that can be publicly accessed through a number of Web sites, most notably the CERHR and FDA sites.

In addition to the extensive CERHR review, the CIR first reviewed phthalates 20 years ago (CIR 1985). Although the group's conclusion—that exposures to phthalates from cosmetics are low compared to levels that would cause adverse effects in animals—has been questioned by the EWG, there is growing evidence (i.e., CERHR, FDA, and IARC conclusions) that the concerns in general over phthalate risk do not have a compelling scientific basis, either qualitatively (relevance of animal data to humans) or quantitatively (wide margins of exposure between effect levels in animals and exposure levels to humans) (CIR 2003).

Parabens

Parabens are frequently identified as agents of possible concern as a result of their alleged "use in more personal care products than any other synthetic ingredient" (EWG 2005). The allegation is that parabens can mimic estrogen and therefore may exert estrogenic effects in humans. The EWG states that associations between paraben estrogenic activity and "breast cancer and altered pregnancy outcomes," although not studied in humans, are firmly borne out by laboratory studies. However, no scientific citations or studies are offered to support this point.

There are available data to address the concern over parabens, similar to those for phthalates. The European Commission Health & Consumer Protection Directorate General recently provided its opinion and conclusions on the safety of parabens. The Commission concluded that parabens (4-hydroxybenzoic acid, and its salts and esters, currently regulated by Cosmetic Directive 76/768/EEC) can be used as a preservative up to a maximum concentration of 0.4% in finished products (for one ester) and up to 0.8% for mixtures of esters (SCCP 2005). It is noteworthy that this opinion emanates from the European Union, a region where safety evaluations of chemicals based on hazard-based analysis, as opposed to risk-based analysis, predominate.

The European Commission has also addressed the issue of breast cancer relative to cosmetic product use and concluded that there is no evidence of demonstrable risk for the development of breast cancer caused by the use of underarm cosmetics (SCCP 2005). Because parabens have been implicated as a possible factor in human cancer, this Commission's opinion was based largely on a review of the toxicological database for parabens, which includes acute, subacute, and chronic toxicity studies in rats, dogs, and mice, and which have demonstrated parabens to be essentially nontoxic, noncarcinogenic, nongenotoxic, and nonteratogenic. Parabens are not bioaccumulative and therefore not expected to remain in human tissues. In vitro estrogen binding assays have confirmed that parabens are capable of binding to the estrogen receptor, but in all cases (i.e., for various different paraben esters), estrogenic potency remains 1000 to 1,000,000 times below the potency of the natural estrogen, 17ß-estradiol (SCCP 2005). In addition, there are in vivo assays that have been conducted with parabens (i.e., those currently recommended for endocrine testing such as the uterotrophic assay), and in all cases, the potency of parabens tested remained several orders of magnitude lower than that of 17ß-estradiol.

In addition to the European Commission's review, two recent epidemiological studies on the use of underarm cosmetics in relation to breast cancer could not establish a relationship between the use of underarm deodorants and antiperspirants and the occurrence of breast cancer (Mirick, Davis, and Thomas 2002; McGrath 2003). Mirick and colleagues (2002) conducted a study on 813 women with breast cancer and found no link between breast cancer and antiperspirants or deodorants.

A recent review article summed up a number of toxicological studies of parabens, and concluded that, based on both

theoretical (estrogenic) and experimental reproductive effects in rodents, further reproductive toxicity studies should be done (Soni, Carabin, and Burdock 2005). These authors did not express concern over likely human health concerns, and pointed out the lack of any basis for fear of human carcinogenicity of parabens.

To summarize, parabens have a long history of safe use, including use in food, and have been specifically recognized as safe by the FDA. The CIR, in 1984, reviewed their use in cosmetics and concluded that they did not pose a risk to consumers. More recently, the scientific literature for several parabens has been extensively re-reviewed (CIR 2004). The available scientific data, including toxicology studies, do not support claims about the risk potentially posed by parabens in cosmetics.

FINAL THOUGHTS

In summarizing this review on the adequacy of safety testing of cosmetics, we can state the following:

- Cosmetic products have a history of safe use, as attested to by decades of use, encompassing thousands of products, and involving millions of consumers.
- Very few incidents of systemic injury involving cosmetics have been reported. The most commonly reported effects include irritation, mechanical injury (e.g., mascara wand scratching the eye), and sensitization. There are no known reports or human data linking cosmetics with cancer, reproductive effects, or genetic damage.
- Cosmetic companies and the industry have responsibility for the safety of their products. Although results of toxicology and safety testing are not always publicly disclosed, cosmetic manufacturers have internal processes, programs, and testing protocols that are designed to ensure the safety of the products they produce. Additionally, the U.S. Food and Drug Administration has oversight and the Cosmetic Ingredient Review makes recommendations concerning the safety of the ingredients used in cosmetics.
- Much of the misperception regarding the safety of cosmetic ingredients stems from the fact that basic principles of toxicology and risk assessment are not applied. Those fearful of cosmetics generally (1) consider hazard only, without evaluating actual exposure; and (2) extrapolate results from high-dose toxicology tests in animals to the trace levels used in cosmetics and assume similarity in response without consideration of the differences in route, duration, and amount of exposure.
- Numerous regulatory and independent bodies (FDA, CERHR, CIR) employ quantitative risk assessment in their evaluation of cosmetic ingredients. This is the currently accepted international approach for safety evaluation as it considers both hazard and exposure; furthermore, this general approach is applied to dosage levels for pharmaceuticals and tolerance limits for pesticides, both of which are highly regulated products.
- The cosmetic industry should be encouraged to publish, for public consumption, the results of its safety evaluation processes undertaken as part of its overall product stewardship efforts. Such transparent disclosure would (1) inform and educate, (2) rebuild trust, and (3) alleviate public anxiety.

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