CTFA TECHNICAL GUIDELINES

CTFA Safety Evaluation Guidelines

CTFA
Cosmetic, Toiletry, and Fragrance Association

CTFA Safety Evaluation Guidelines

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Foreword

In 1969, CTFA began publishing its *Technical Guidelines* in the *CTFA Cosmetic Journal.* These guidelines were developed by the newly organized CTFA Microbiology Committee and were concerned with microbiological issues. The benefits of having the *Guidelines* available in a single volume, and presented in a standardized format, were recognized, and in 1974, the first independent compilation of the *Technical Guidelines* was published.

After several major revisions and additions to the *Guidelines*, CTFA responded to requests made by the users and split the *Guidelines* into separate volumes so that individuals might purchase sets relating specifically to their areas of responsibility. The *Guidelines* are now published by CTFA in three volumes: Microbiology, Quality Assurance, and Safety Evaluation.

The *CTFA Technical Guidelines* are dynamic documents that undergo extensive development and review prior to publication by CTFA technical committees and staff, as well as public review by CTFA members and nonmember companies, federal government agencies, and scientific professional societies. Comments from individuals are welcome at any time.

While CTFA has sought to ensure that these *Guidelines* generally satisfy applicable U.S. federal statutory and regulatory requirements as of the date they were drafted, CTFA can assume no responsibility for their adequacy, nor does it purport to advise as to the necessity for their use in any particular situation. In those *Guidelines* that address regulatory requirements, decisions such as when a report must be filed and what information must be included in it can be made only by those individuals responsible for making such submissions. With regard to all of the areas covered by *CTFA Guidelines*, each company must independently assume responsibility to ensure that their conduct is consistent with all current, applicable federal, state and local laws and regulations.

It must be emphasized to the user that these *Guidelines* are intended only to aid manufacturers in developing programs that meet their individual needs. The *Guidelines* must not be considered either minimum or maximum requirements of effective programs. Alternative ways to reach the goals of the *Guidelines* may well exist and may be equally useful. *Guidelines* on any topic must, of course, be adapted to the particular operations of the manufacturer using them.

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Introduction

The goal of any cosmetic[1] product safety evaluation and substantiation is to ensure that a product will be safe for consumers under the expected, recommended, and/or customary conditions of use, as well as under reasonably foreseeable conditions of misuse. Competent and trained scientific personnel should constantly assess the relevance of the latest toxicological and medical literature, changing safety evaluation techniques, changes in the regulatory environment, and marketing history of the product under normal use conditions. Also, they should be continually alert to examine the relevance of safety issues relating to a specific ingredient or product, and should reassess their safety if new and unforeseen effects come to light. Safety testing may be warranted when the existing information is not adequate to support the safety of an ingredient or product or when new safety issues arise. Even when meaningful safety data exist, testing may be useful to provide confirmatory evidence of the safety of an ingredient or product.

Every cosmetic product contains a combination of ingredients. It is generally possible to assess the safety of a formulation by analyzing the relevant toxicological endpoints of each ingredient in relation to the expected product exposure. The safety assessment of finished cosmetic products takes into account a number of different things, including the physical-chemical data and chemical structure of the ingredients, toxicological data on ingredients, *in vitro* and clinical tests conducted on the final product, and potential product exposure. Confirmatory testing of product compatibility and acceptability on human volunteers may be subsequently undertaken.

The *CTFA Safety Evaluation Guidelines* provide manufacturers of cosmetic, toiletry and fragrance products guidance in the use of pre-clinical and clinical safety testing as a means to substantiate the safety of both ingredients and finished cosmetic products. Pre-clinical testing may include animal testing, generally following regulatory guidelines, as well as *in vitro* alternative methods using cell, tissue, and organ culture. In silico methods, in which computer predictions are made using structure-activity relationships, may also be part of the safety evaluation. Clinical testing involves testing with human volunteers under controlled conditions.

The responsibility for ensuring the safety of cosmetic products rests with the manufacturer and/or distributor. In the U.S., FDA regulations require cosmetics to be adequately substantiated for safety or labeled with the statement: "Warning – The safety of this product has not been

[1] The *CTFA Safety Evaluation Guidelines* are specifically designed to address cosmetics, defined by the Food, Drug & Cosmetic Act, sec. 201(i), as "(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles." Portions of the Guidelines may also be relevant to cosmetic-drugs, which are products with both a cosmetic and a drug function (examples are antidandruff shampoo, toothpaste containing fluoride, or moisturizers and makeup marketed with sun-protection claims). However, the active ingredients in cosmetic-drugs require pre-market approval and these Guidelines are not intended to address those regulatory requirements.

determined" (21 CFR 740.10). Some considerations relevant to safety assessment can be found in articles cited in the preamble to the FDA cosmetic regulations (Giovacchini, 1969; Giovacchini, 1972). All other regulatory requirements must also be satisfied. These include, but are not limited to, prohibition of the use of certain ingredients in cosmetics (21 CFR 700); the requirement that color additives be FDA-listed; the certification of individual batches of certain color additives (the "certified colors"); and the need for tamper-resistant packaging for certain products (21 CFR 700.25).

Product manufacturers should first consider the need for such safety testing, taking into account various factors, including the available toxicology data on the individual ingredients in the product (and on products similar in composition to the product being evaluated), *before* undertaking any testing program. These *Guidelines* include brief descriptions of a number of standard toxicology test procedures applicable to products and/or ingredients.

These *Guideline*s are not intended to establish industry testing standards for cosmetic, toiletry and fragrance ingredients or products. Rather, the *Guideline*s can aid in the selection and design of appropriate safety test procedures, and identify representative tests that, in the judgment of trained industry toxicologists, can be used to substantiate the safety of ingredients and finished products. There may also exist variations of the tests described, or other equally relevant and meaningful tests, that competent and responsible scientists may conclude are acceptable to judge particular aspects of product safety.

The cosmetic industry is committed to the development, use and validation of animal alternatives, and has put extensive resources towards developing alternatives to animal testing procedures over the past twenty years. During this period, organizations were established in both the United States (Interagency Coordinating Committee for the Validation of Alternative Methods [ICCVAM]) and in Europe (European Center for the Validation of Alternative Methods [ECVAM]) as resources for the evaluation, validation and regulatory acceptance of new alternative test methods. Scientific evidence of the ability of an alternative test to predict the toxicity of an ingredient or finished formulation is of fundamental importance (ICCVAM, 1997; ICCVAM, 2003). Data from alternative tests, which are usually *in vitro* procedures, may contribute to the final judgment on the toxicological potential of an ingredient or to the overall safety of the finished product. While few of these alternative procedures have been fully accepted by regulatory agencies at the current time, the results of such testing are useful as screening tools or as part of a comprehensive safety program.

Guidelines cannot substitute for day-to-day familiarity with the principles and the continually evolving science of toxicology and safety evaluation. To ensure the reliability of testing, studies should be designed, monitored, and the results interpreted and evaluated by persons who are trained and experienced in toxicology and safety evaluation. Such persons should have a fundamental understanding of cosmetic, toiletry and fragrance ingredients and products, and of the tests being used. In the case of animal testing methods, they should have knowledge of the proper and humane use and care of laboratory animals, and of Good Laboratory Practices (GLP). Numerous guidance documents have been published on the humane care of laboratory animals (NIH, 1996) and GLP regulations have been established by the FDA (21 CFR Part 58). Animal alternative tests may also be performed under GLP regulations. In the case of human testing, an awareness of ethical considerations and knowledge of applicable clinical testing regulations, such as Good Clinical Practices (GCP), are needed (21 CFR Part 50; 21 CFR Part 56; ICH, 1996).

The *Guidelines* address the steps that should be taken in the safety evaluation of a cosmetic ingredient or product. Each component of a risk assessment - hazard identification, dose-response assessment, and exposure assessment – is critical in evaluating the potential risks from using these products. The concepts presented are universal in their application for assessing the hazards and risks of chemicals in a variety of industries. Risk management, the process by which policy actions to deal with the hazards identified in the risk assessment are chosen, is discussed briefly but is equally important in the overall safety evaluation process. The reader is encouraged to consult the references listed at the end of this *Introduction* for further information on the conduct of safety and risk assessments.

HAZARD IDENTIFICATION

A first step in the evaluation of the safety of a finished cosmetic product is to review the toxicological profiles of the ingredients. Cosmetic products are combinations of synthetic or natural chemical ingredients. Therefore, the careful selection of ingredients is a primary consideration in ensuring the safety of finished cosmetic products. As part of the selection process, one must consider industry and regulatory standards as well as legal requirements associated with certain ingredients.

The Cosmetic Ingredient Review (CIR) is one valuable source of information on ingredient safety specific to cosmetics. The CIR was established in 1976 by CTFA to review and assess the safety of ingredients used in cosmetics in an independent, unbiased and expert manner. Seven scientists serve on the CIR Expert Panel, selected from the disciplines of dermatology, pharmacology, chemistry, toxicology, and pathology. Three non-voting liaison members represent the U.S. FDA, the Consumer Federation of America, and CTFA. The Expert Panel may affirm the safety of ingredients as used, or may conclude safety with certain qualifications such as concentration limits or use in restricted product types. They may also conclude that the use of certain ingredients in cosmetics is unsafe, or that there are insufficient data to assess safety. For more information, see http://www.cir-safety.org.

The structure of a chemical reflects its chemical and biological reactivity and needs to be considered when assessing a new chemical entity, a new use for a currently used (existing) ingredient, or an increase in the concentration of an existing ingredient. As an initial evaluation, a structure-activity evaluation should be conducted to determine if any structural alerts for a toxic endpoint are present. Structure-activity relationship (SAR) evaluations are generally conducted utilizing commercially available computer software. It is also necessary to consider the degree of chemical purity and stability; possible interactions with other ingredients in the finished product; the potential for systemic bioavailability via dermal and/or mucous membrane penetration, oral ingestion, or inhalation; and metabolism. The presence of impurities is often technically unavoidable but these impurities must be of no significant toxicological relevance in the finished product. The quality of the available toxicological information for ingredients must be taken into account. Data quality varies depending on whether one is dealing with chemical substances, plant extracts, other natural ingredients, complex mixtures or perfumery compounds.

DOSE RESPONSE ASSESSMENT

Of fundamental importance in conducting a safety evaluation is an understanding of the dose-response for adverse effects of individual ingredients. Analysis of the toxicological data begins by identifying the adverse effect which is seen at the lowest dose in a relevant experimental animal

model, e.g., the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL). As part of this dose-response assessment, the relevance of the biological response to humans must be understood. Clinical data may also be used in determining the potential for human relevance for a possible biological effect. Identification of the NOAEL or LOAEL represents an initial step in the risk assessment. As described later under Risk Assessment, safety factors or computer-assisted models can then be used to determine acceptable exposure levels. Pertinent information on the absorption, distribution, metabolism, and elimination (ADME) of the ingredients can also be incorporated into the toxicity assessment to refine acceptable exposure levels.

Once the assessment of each of the ingredients in a product is completed, the entire makeup of the final product must be considered, including the potential for possible ingredient-ingredient interactions, or ingredient-packaging interactions, leading to unexpected toxicological or adverse effects. The potential for an increased rate of penetration needs to be assessed. With most finished products, confirmation of predicted safety for skin effects is accomplished with testing on human volunteers. This frequently includes testing for dermal irritation and sensitization. Testing on humans requires close monitoring for any undesirable effects which may occur. Such tests must necessarily be made on a limited number of volunteers, with appropriate medical supervision and with respect for ethical considerations and Good Clinical Practices. Such results must also be interpreted by trained individuals knowledgeable with the test methodologies used.

EXPOSURE ASSESSMENT

Ultimately, a safety assessment must provide adequate substantiation that a cosmetic product can be used safely by the consumer under the expected, recommended, and/or customary conditions of use, as well as under reasonably foreseeable conditions of misuse. Intentional product abuse should also be considered, although the ability of a manufacturer to control for this may be limited. Determining exposure is an important component in the overall assessment of product safety, and must be done on a product-by-product basis with secondary exposures (e.g., inhalation with hair spray use or ingestion from lipsticks, etc.) taken into consideration.

Factors to be considered in determining exposure levels for products and ingredients include, but are not limited to:

- Product type
- Amount used per application
- Frequency of application
- Site of body contact
- Duration of product contact
- Concentration of individual ingredients in the final product
- Use by sensitive subpopulations (i.e., babies, the elderly, pregnant women)
- Method of application
- External factors, i.e., sunlight exposure
- Variation in use related to weather
- Local or temporal habits and trends
- Cultural considerations
- Conditions of foreseeable misuse

RISK ASSESSMENT

Following the collection of toxicology data and the exposure assessment, the next phase of the safety evaluation process is determining if there is any potential health risk to consumers. Numerous compendia on conducting risk assessments have been written, and there remains a scientific debate on the best approach (Barnes and Dourson, 1988; Faustman and Omenn, 2001; Rodricks et al, 2001). A margin of safety approach (i.e., identifying the NOAEL, then applying a safety factor to it) is a generally accepted method for safety assessment. This approach is typically used in the evaluation of individual ingredients using systemic toxicity data, and assumes the underlying mechanism of toxicity supports the existence of a threshold dose.

Margin of Safety Approach

To use the margin of safety approach, the lowest (most conservative) NOAEL is identified from animal studies or human data if available. Additional safety factors are then applied to the NOAEL. A factor of ten is typically applied to account for interspecies differences (unless the NOAEL is based on human data), and a second factor of ten is applied to account for intra-species variation. Therefore, the identified safe dose is 100 times lower than the dose at which no effects are observed. A third factor of ten may be applied if the study used to determine the NOAEL is of short duration, or if the study determined a LOAEL rather than a NOAEL. The identified safe dose is then compared to exposure to assess whether there is a potential safety issue. Alternatively, computer assisted modeling as a means for assessing risk is becoming more widely used. Regardless of the approach, the method used should be well documented as well as scientifically rigorous. Professional experts should be consulted for complex risk assessments.

A margin of safety approach is also generally applicable to non-systemic toxicity endpoints, such as skin irritation, but risk assessment criteria are more subjective, and safety factors are less clearly defined. Interpretation of results must take into account the test design. For example, the dose per unit area applied and the effect of occlusive conditions, if used, must be factored into the interpretation of skin testing results. The results of *in vitro* tests which are used more commonly in the assessment of non-systemic endpoints do not easily lend themselves to a quantitative risk assessment. Data from studies in human volunteers may be incorporated, including market research employing subjective diaries and questionnaires obtained during the conduct of 'home placement' studies, 'mall-intercept' tests, and focus groups. This type of data will not be available for systemic toxicity endpoints. Prior experience with similar formulations is typically considered in the risk assessment process.

RISK MANAGEMENT

Once the risk assessment of the ingredient or finished product is completed, the results may require the implementation of a risk management process. Each manufacturer must decide what policies are most appropriate with respect to their risk assessment. Risk management actions could include labeling changes, label warnings, or formulation changes. In all cases, cosmetic products must be safe for their intended use and possible foreseeable misuse.

POST-MARKETING SURVEILLANCE

Once a product is in the market, an active and structured surveillance of consumer experience during use can be used to confirm product safety. For most products, the marketplace represents a much larger and diverse population than any of those used to evaluate a product during pre-market activities. Therefore, unanticipated safety-related concerns with a product are possible. A manufacturer and/or marketer should establish post market surveillance processes for the identification of safety issues related to their products beyond serendipitous discovery. A properly structured surveillance process will also help identify consumer use patterns, such as alternate uses or product combinations, which may contribute to adverse events.

The optimum post market surveillance process includes a regular survey of consumer contacts received by a marketer or manufacturer either through toll-free numbers on packages or direct correspondence. Trend analyses of contact data, including evaluations of any reported adverse events, as well as comparison of these trends with historical information for other comparable products, represent the best mechanisms for identification of safety-related concerns.

A manufacturer can also place the American Association of Poison Control Centers (AAPCC) nationwide telephone number on the product label (1-800-222-1222). This telephone number provides access to 62 US poison control centers nationwide. There is no charge to place this number on a product label; however, specific guidance recommendations must be followed. The requirements are detailed at the AAPCC website (www.aapcc.org).

The services of a poison center or health information service can be contracted to manage consumer contacts regarding adverse events. There are advantages to contracting with an individual service rather than the national poison center number including: 1) responses to non-emergency product inquiries and consumer complaints; 2) customer-specific data for each consumer contact; 3) additional data collection beyond those of the AAPCC; and 4) potential source of consulting services for labeling, product safety, and regulatory issues.

Additional external sources of information regarding the safety of marketed products are detailed in Table 1-A. These sources can add overall understanding of adverse events for consumer products (Toxic Exposure Surveillance System), packaging injury complaints (National Injury Information Clearinghouse), as well as intentional abuse of products containing alcohol or propellants (National Center for Health Statistics and the Drug Abuse Warning Network). Finally, medical literature (human and animal) can provide more in-depth reports with details on an injury but are often lacking on circumstance information (and confirmed relationship to product). Media clipping services as well as surveys of product liability claims can also serve as sources of information.

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EXTERNAL SOURCES OF SAFETY INFORMATION - MARKETED PRODUCTS

Public Information Source	Access	Summary
Toxic Exposure Surveillance System (TESS)	The American Association of Poison Control Centers www.aapcc.org/poison1.htm	TESS represents the only comprehensive poisoning surveillance database in the United States. It contains detailed toxicological information on more than 2 million poison exposures reported to U.S. poison centers annually.
National Center for Health Statistics Mortality Data from the National Vital Statistics Systems National Hospital Discharge Survey	U.S. Department of Health and Human Services, Center for Disease Control www.cdc.gov/nchs	Mortality Data from the National Vital Statistics Systems represents data from the 50 states and 5 territories. These statistics are a source of demographic, geographic and cause of death information. Both preliminary and final annual data are available. The National Hospital Discharge Survey (NHDS) represents an annual survey of hospitals which uses sample selection, medical transcription and automated medical record data. Medical information on patients includes diagnoses and procedures.
National Injury Information Clearinghouse	U.S. Consumer Product Safety Commission (CPSC) clearinghouse@cpsc.gov www.cspc.gov/about/clernghse.html	This clearinghouse collects and disseminates information on the causes and prevention of death, injury and illness associated with consumer products. It compiles data obtained from accident reports, consumer complaints, death certificates, news clips, and the National Electronic Injury Surveillance System operated by the CPSC. Publications including statistical analysis of data are available in serial publications from the CPSC.
Drug Abuse Warning Network (DAWN)	Substance Abuse and Mental Health Service Administration of the U.S. Department of Health and Human Services www.dawninfo.samhsa.gov	DAWN collects data on drug-related visits to a sample of the Nation's emergency departments and drug-related deaths from medical examiner and coroner (ME/C) jurisdictions throughout the country. Data are a retrospective review of patient medical records including illegal drugs of abuse, prescription and over-the-counter medications, dietary supplements and non-pharmaceutical inhalants.

Table 1-A