



CHEMICAL REACTION BY STEVE HERMAN

Safety First

Safety testing for irritation or toxic activity can give a strong indication in cell culture of what could happen to a human.

What is it that is not a poison? ... Only the dose decides that a thing is not poisonous.

—Paracelsus

"A MEDICAL STUDENT, an oarsman, a tenor, a shouting politician, a small landlord, a small investor, a drinker, a good fellow, a storyteller, somebody's secretary, something at a distillery, a tax gatherer, a bankrupt and, at present, a praiser of his own past." James Joyce's description of his father may not reflect in its details the activities of a toxicologist, but it does reflect the range of activities falling under the domain of toxicology: "A chemist, a biologist, a biochemist, a student of genetics, a user of knock-out mice, a statistician, a maker of graphs, a communicator of results, a developer of methods, an adept in skin physiology and praiser of his test results."

One universal feature of the modern cosmetic and fragrance industry is a concern for safety. Trust in product safety is essential for maintaining consumer and governmental confidence. The cosmetic industry, guided by the Cosmetic, Toiletry and Fragrance Association (CTFA), tests raw materials and publishes the results through the efforts of the Cosmetic Industry Review (CIR). The fragrance industry, under the leadership of the International Fragrance Association (IFRA) establishes safety standards through the activities of the Research

Institute for Fragrance Materials (RIFM). The safety of thousands of materials intended for personal use is not easy to determine, and the needs of the industry and the consumer, as well as the science that can be brought to bear on the subject, are in constant evolution. The internationalization of safety

TABLE 1: SELECTED VALUES OF LD₅₀

Chemical	LD ₅₀ (mg/kg)
Ethyl alcohol	10,000
Sodium chloride	4,000
Caffeine	192
Arsenic trioxide	20
Nicotine	1
Rattle snake venom	0.24

issues has created a new layer of complexity on an already complex landscape, making decrees by SCCNFP a part of our everyday concerns—once we figure out what SCCNFP is! Don't run to the Internet, it translates to the Scientific Committee on Cosmetic and Non-Food Products Intended for Consumers.

The basis of safety testing is the science of toxicology, which can be defined as the study of the adverse effects of substances on living organisms. The name derives from the Greek word "toxon," which means "bow." The Greek historian Herodotus used the word "toxikon" to describe a poison arrow, indi-

cating an early application of chemical warfare.

There are many forms of chemical exposure: ingestion, inhalation, dermal/topical and parenteral, such as intravenous, intramuscular or intraperitoneal. Tests that may be appropriate for cosmetic products include eye irritation, oral toxicity, skin irritation, photo-toxicity and carcinogenesis. Three classifications of testing are considered: in vivo (tested on live animals), in vitro (usually tested on cell cultures) and ex vivo (tested on biopsy or slaughterhouse material). Although establishing the safety of raw

materials or finished products was once based on animal testing, public opinion has essentially eliminated that avenue unless it is absolutely necessary.

In an earlier era of toxicity testing, the LD₅₀ was a primary test, LD standing for lethal dose. It indicated the amount of material that, when ingested, would kill half the test animals. The LD₅₀ of some familiar materials is shown in Table 1. The dose concept, as Paracelsus noted, is at the very heart of toxicological methodology. Many essential nutrients, such as vitamin A, can be fatal at high doses. Substances that can harm following exposure to very small amounts are branded to

FIGURE 1: EFFECT OF TOXIC DOSAGES

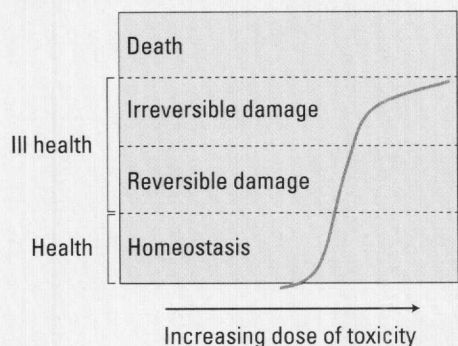
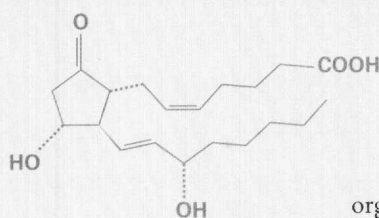


FIGURE 2: STRUCTURE OF PROSTAGLANDIN E₂



be extremely toxic; those that require many grams to cause harm are identified to have low toxicity. A diagram of the effect of dosage is shown in Figure 1. Increasing doses of a toxicant can lead to reversible damage, irreversible damage and even death; homeostasis is the condition of an organism in a healthy state of physiological equilibrium.

While animal testing—as well as human testing—is kept to a minimum, a steady progression


of new techniques has refined testing in a socially sensitive way over the past few decades.

It is important to identify cosmetic ingredients or products that are an irritant. When an irritant invades the stratum corneum and epidermis it triggers the release of histamines, prostaglandin and cell mediators such as interleukins. These chemicals can be detected by several methods, including Enzyme-Linked Immunosorbent Assay (ELISA), a fundamental tool of clinical immunology.


The immune system has many different types of cells that act together to take care of unwanted infections and altered cells. Interferon is a natural substance produced by the body in

response to infection and disease, and cytokines are the chemicals produced by these cells that orchestrate the attack. Just as hormones in the endocrine system can produce an effect on other cells, so cytokines can act on other immune cells, especially cells that are close by. As numerous cytokines were discovered, nomenclature became a problem, so new ones were named interleukins and numbered as they were discovered, IL-1 being the first one in a list that has reached IL-18.

Prostaglandins are cell messengers produced in the cell membranes by the action of enzymes on essential fatty acids. They were first isolated from



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semen in 1936 by van Euler, who assumed they originated in the prostate, hence their name. Prostaglandin E₂ (PGE₂) is particularly involved in early inflammatory events. Its structure is not overly complex, as can be seen in Figure 2.

ELISA, which is based on the principle of antibody-antigen (lock-and-key) interaction, will detect the release of PGE₂ and interleukins IL-1 α or IL-8. ELISA tests can be correlated to human irritation from surfactants, skin care products, color cosmetics and hair dyes. ELISA makes the testing of large numbers of materials reliable, in a time- and cost-effective way.

All this jargon can be intimidating, but the basic lesson is simple. The chemistry of irritation or toxic activity can give a strong indication in cell culture of what could happen to a human. The test methods allow alternatives to animal testing, and as knowledge of the biochemical pathways progresses, the ability of toxicologists to predict in vivo results from in vitro testing improves accordingly.

The Roman poet and philosopher Lucretius had his own view of toxicology, "What is food to one may be fierce poison to others." This, combined with the dose principle of Paracelsus, augmented by some modern chemistry, biology and instrumental methods, plus knowledge of regulatory and social concerns, form the basis for understanding safety testing. And don't forget the knock-out mouse, a genetically altered mouse used to examine the pathophysiology of disease and test therapeutic approaches. These mice are one of the ultimate tools of modern biotechnology. Toxicology, a necessary adjunct to responsible personal care development, is a fascinating field operating close to the edge of our knowledge of the nature of life itself. 

Acknowledgment

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