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# Safety of Industrial Chemicals and Finished Product

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ABSTRACT

The chemicals present in cosmetics, detergents, and other household products, pesticides, solvents, etc., are handled by industrial workers who are engaged either in their production or applications, thereby getting exposed to their toxicity. The general population also do come in contact periodically with various chemicals which cause adverse effects on the body. Therefore, it is necessary that safety evaluation be carried out on individual chemicals, as well as on various products that contain combinations of chemicals commonly involved in industrial worker exposure, and general population exposure.

**Keywords:** Chemical safety, Dermal toxicity, Skin irritation, Skin sensitization

## Drug Index Terms

*Industrial Chemical - Drug Toxicity; Cosmetic; Detergent; Domestic Chemical; Pesticide; Solvent*

## Medical Index Terms

*Safety; Industrial Worker; Occupational Exposure; Population; Environmental Exposure; Toxicity Testing; Corrosion; Skin Allergy - Diagnosis; Phototoxicity; India; Standard; Experimental Animal; Guinea Pig; Skin Sensitization; Skin Test; Medical Ethics; Human Versus Animal Comparison; Human; Nonhuman; Rat; Animal Model; Article*

## EMBASE Classifications

### 035 - Occupational Health and Industrial Medicine; 052 - Toxicology

## Introduction

Man is exposed to a number of natural and synthetic chemicals during the course of his lifetime. Many new chemicals are constantly being manufactured, and are widely distributed each year. It is

essential, morally and legally, that chemical safety be examined for their proposed use, and appropriate warning be issued of potential harmful properties of the chemical on short or long term use. The term "chemical" covers a wide range of substances including cosmetics, household products, industrial and domestic cleaning products, medicines, pesticides, fertilizers, solvents, and a large number of substances used in manufacturing operations. At every step in the manufacturing process, or transport, storage, use and disposal of chemicals, there is possibility of close body contact. Hence without protective equipment, the chances of toxicity resulting from skin contact is quite high. Safety evaluation prior to use of unknown chemicals is essential.

The safety of cosmetic products is very important because of their widespread use. Today, cosmetic products find an inalienable place in the normal everyday life of most people for grooming various parts of their body such as hair, skin, and teeth. Although manufacturers of cosmetics generally take care to ensure continued safety in the use of these products, it is not possible to ensure zero risk or absolute safety for any product. Finished cosmetic products are only tested on animals if the new formulation significantly differs from previous preparations. Moreover, it is largely restricted to the investigation of effects on skin and mucous membranes.

It is rare for a new substance to be introduced specifically for use only in cosmetics. It is much more common for existing chemicals that are already in use for other purposes to be introduced into cosmetic products. Where however, a totally new chemical is involved, certain toxicological tests have to be conducted.

## Occupational exposure in the manufacturing plant

Before a new ingredient is introduced into a manufacturing plant, the likelihood of exposure, and potential hazards resulting from such exposure to employees from both the new raw material and the final product containing it have to be evaluated. Effects from repeated exposure by skin contact, inhalation or even repeated ingestion of small amounts are to be assessed. Clinical tests involving human volunteers should be done for evaluation of effects on skin[1].

In many cases, toxicological data do not exist either for an ingredient or for a finished product. Safety assessment is a continuous process. Changes in usage pattern, exposure conditions, and the availability of more sophisticated toxicity rating techniques play an important part in the continuing assessment. Consumers' feedback regarding the safety or toxicity of products also has to be carefully followed up. Dermatological observations are important, and may reveal that a product which was considered safe when initially introduced in the market actually has harmful effects with extended use.

The safety evaluation of a new chemical should be integrated with the proposal for production, particularly if it is intended for a large consumer market. Various toxicological techniques have been recommended for safety evaluation of chemicals[2]. Legislations have been enacted on the safe use of chemicals, the tests required to be carried out to identify adverse effects, and to ensure safety of chemicals to the consumers. It is generally considered that the protocols and experimental practices used by the USA and UK are acceptable in a broad manner, and national variations tend to be minor in nature. However, ethnic, climatic, nutritional and other factors may play an important role in the toxicity response of chemicals.

## Toxicological tests to predict adverse effects on skin

Adverse effects on skin can be identified by routine tests. They are usually designed to study the following -

Irritation

Allergic contact dermatitis

Non-immune contact urticaria

Anaphylactic-type allergic sensitization

Phototoxicity, photoallergy and photomutagenicity

Toxicokinetics, study of percutaneous absorption, metabolism, tissue deposition or excretion of the test substance

Dermal toxicity; Systemic changes resulting from skin penetration.

## Tests to classify irritant / corrosive substances

The standard test to determine the irritant potential of a chemical is the application of 0.5ml or 0.5gm under a semi-occlusive patch for 4 hours to the clipped skin of albino rabbits, after which the site is examined at 30 to 70 minutes daily, up to 72 hours. Protocols from different agencies show some deviations in a comparison of the results from 56 substances tested by three different methods. Various factors which may affect the test results include the method of preparation of skin, phase of the hair growth cycle, physical state of the test substance, nature of path, and the criteria used to assess the reaction[3]. The response is recorded by indexing scores of severity of defined features as first presented by Draize et al (1944) and subsequently modified by FDA, USA[4].

The discrepancies inherent in any one protocol may be overcome by testing a substance in duplicate on each rabbit and comparing the results with the response to a control substance. This modification overcomes variations due to differences in susceptibility of various individuals.

In addition to the standard test on rabbits some laboratories have developed other methods to mimic human exposure more closely. One such method is the application of substances to the clipped skin of rats 1 to 4 times per day for 4 days. The effect is observed microscopically, and may be examined in more detail histologically. Strict requirements on the age of rats, method of application, and use of controls are necessary for consistent results. This method is particularly useful to examine the effects of repeated exposure to personal hygiene and household products.

## Predictive tests for allergic contact dermatitis

Delayed hypersensitivity contact dermatitis is a common occupational disorder. Workers in many industries come in contact with many chemicals, either occasionally or frequently. Farm workers are exposed to a number of allergenic substances such as pesticides, fertilizers, etc. Similarly, there are a number of elements which come in contact with the skin in the domestic set up. To advise protection for occupational and domestic exposures, predictive tests are essential.

Predictive tests are done on albino guinea pigs. Sensitization is induced with and without adjuvant by injection or topical application of the chemical. There are a number of techniques for sensitivity tests. The preferred procedure is the Maximization or M & K test, in which the test substance is injected intradermally with and without Freund's adjuvant in the nuchal region, boosted 7 days

later by topical application over the injected site, and after 14 days challenged by a patch test at a separate site[5,6]. The induction concentration is the threshold for irritation. The challenge concentration is non-irritant. However, when examining potent allergens, the concentration of the test substance for induction and challenge are to be predetermined. Repeat challenges on sensitized animals may be made to detect cross-reactions with other chemicals or impurities, or allergic expression of ingredients in formulations, or to determine dose responses.

Two other methods are sometimes used instead of the Magnusson and Kligman test, and are claimed to be more representative of human responsiveness.

*Cumulative contact enhancement test:* Guinea pigs are treated twice weekly for 2 weeks by 24 hour applications of the test substance, with an injection of Freund's adjuvant at the test site[7].

*Buehler test:* Occluded patch applications are given once weekly for 6 hours, for three weeks to induce sensitization without any treatment with adjuvant[8].

## Phototoxicity

Some substances that are normally innocuous to skin may become photo-activated in the presence of light of a particular wavelength to form photobiologically active products. It is important to screen substances likely to come in contact with the skin for their ability to absorb light in the range of 280 to 800 nm. These substance which absorb light, particularly in the UVA-UVB range, are potential agents which may cause photobiological effects. Light induced reaction of a substance may be of two types: photoirritation or photoallergic response. Some people prefer to use the term phototoxicity for photoirritancy, whereas others consider all adverse responses to light activated substances as phototoxic. Photomutagenicity and the development of in vitro cell methods for its detection have acquired much interest in the past few years.

Photo-irritant tests are preferably done using albino guinea-pigs or rats. The test animals should be 3 to 4 weeks of age, because at this age the hair is in telegen phase. The hair is clipped, and the test substance gently applied to the skin and left for 20 minutes, after which it is wiped using the solvent. The site is irradiated by fluorescent blacklamps with an emission spectrum of 300 to 400 nm for 3 hours. The changes in the skin are observed at intervals up to 96 hours, and skin reactions are scored for degree. Consistent results are obtained when non-irritant amounts of substances or exposure to light are used even when the test is performed on different species, e.g., man, pig and mouse[9].

In photo-allergic induction, light transforms a prohapten in the test substance into a hapten, which combines with protein of the skin or deeper tissue to form the allergen. The most discriminating methods are those using Freund's adjuvant, and do not differ greatly in principle from that for the contact allergy test. Repeated applications of test substance to a shaved skin site are made. After an interval of 2 weeks, the animals are challenged to application of the test substance to a fresh skin site, and irradiated with UVB,UVA, and visible light, and may be challenged a second time omitting UVB. A modified method enables a concomitant test for photo-irritant and photo-allergic potential.

## Testing procedures recommended by Bureau of Indian Standards (BIS)

The following procedures have been recommended by the BIS for testing of a finished product for its safety evaluation when it comes in contact with the skin[10].

### 1. Skin irritation test (Guinea pig immersion test)

In this test, six albino guinea pigs are clipped free of fur on the back and lateral abdominal areas. The animals are then immersed in 1% suspension of the chemical for one hour daily for four consecutive days. Twenty four hours after the last immersion, the reactions on the skin of the guinea pigs are read and the primary irritation index (PII) is calculated.

Mortality, if any, and the body weight of the guinea pigs are also noted.

### 2. Skin sensitization test

In this test, the guinea pigs are given intradermal injections on the clipped back with a predetermined dose of the chemical. After one week, the animals are given boosting dose of slight irritant concentration. Two weeks after boosting the animals, the chemical is applied on the flank at non-irritant concentration. The readings of the reactions (erythema and /or edema) are taken after 24 and 48 hours.

### 3. Repeated insult test

Ten human volunteers are asked to dip their hands in 1% suspension or solution of detergent, or any other chemical likely to come in contact with skin daily in the course of work, for half an hour daily, for 5 days a week. The reactions are noted with reference to erythema, edema, itching, cracking, and scaling.

## Ethical considerations

While taking up studies on human volunteers it is the responsibility of the investigator to take all precautions to avoid the possibility of any undesirable effects on them. To ensure this, the investigator should

• carefully consider the chemical structure of the ingredients and assess the potential risks

• take into account all the toxicological data available on the ingredient and where appropriate on structurally related materials, and take necessary precautions so that no significant risk to the volunteers is involved in the proposed study.

If any unusual risk to participants is involved, the investigator should submit plans for the study to an ethical review committee. Such a committee will review aspects of a study which may affect the well-being of participants, but even then, the final responsibility for a study remains with the investigator.

The most important ethical consideration is that the study should not adversely affect the health of the volunteers.

Ethical requirements which should be taken into consideration in the planning of studies on humans include the following:

Before any volunteer is exposed to the ingredient, all relevant information on the safety /risk should be obtained.

All participants should be informed volunteers selected after application of inclusion /non inclusion criteria.

All necessary care should be taken to avoid excessive skin reaction.

## Comparison between animal and human studies

Since there are a number of methods used for safety evaluation of industrial chemicals, the action of chemicals is first assessed on the skin of animals, e.g., guinea pig, rabbit, rat, etc., and then on human skin, to further confirm the dermal effects. In animal studies, the exposed skin can be cut for biochemical and histopathological studies, whereas in human studies it is only the visual assessment that can be recorded. In other words, animal experiments can give much more information about the effects of chemicals on the skin.

The bottom line is that products and /or chemicals to be introduced for human use should be free from any kind of toxicity, and this can only be ensured by safety evaluation tests.

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