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Toxicological Considerations in the Use of Consumer Products

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ABSTRACT

Reviews different methods of screening carcinogens by using *in vitro* and *in vivo* carcinogenicity tests. Elaborates on naturally occuring carcinogens in food materials, in working environment and consumer products like dyes. The effects of various consumer products like oils, fats, protein foods and non-metallic and metallic substances used in consumer products have been reviewed. The long-term effects on skin such as dermatitis and irritation due to various chemicals used in consumer products have been elucidated. The effects of tetratogens and hazards due to packing materials have also been examined. Finally, the need for safety in raw materials has also emphasised as important for elimination of toxic effects.

1. INTRODUCTION

Typhoid, bacillary dysentery, cholera, vomiting and diarrhoea due to Staphylococcal infections can all produce havoc when infected food or water are consumed. These diseases are particularly dreaded because their spread from person to person can be rapid, leading to severe morbidity and mortality which can assume epidemic proportions, if control measures are rapidly instituted. Similarly chronic illnesses such as amoebiasis or jaundice (infective hepatitis) can take their toll due to protozoal or viral contamination of food.

Apart from the biological hazard, attention must also be paid to the intake of chemicals whether consumed in food or through externally applied products.

Prehistoric man in his quest for food learnt to discriminate between harmful (poisonous) and harmless or desirable types.[1] Knowledge about toxic effect of animal venoms and poisonous plants was gained and made use of for hunting and fighting. Hemlock, became the state poison of Greeks; aconite, an arrow poison of the Chinese;

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and opium began to be used as a poison as well as antidote.[2] Old medical records[2] mention substances similar to belladona and digitalis alkaloids. Hippocrates around 400 BC added a number of poisons and later (50 AD) Dioscorides – a Greek physician classified systematically, the poisons into those of animal, plant and mineral origin.[3] It was in the 16th century that the dose-response relationship of toxic substances was first introduced by Paracelsus which became the most important principle in Toxicology[4], viz. everything is a poison, only dose determines what is poison and what is not.

As the era of modern toxicology ushered in, the classification of substances with a strict line of demarcation into beneficial ones and harmful ones became an unreality. Even water can be shown as a harmful substance and an arrow poison such as curare can be shown as beneficial under a set of contrived conditions. Hence it is apparent that the harmfulness or safety in use of a substance is related primarily to the amount (dose) of that compound that is introduced into the living system.

It is in this perspective that one should examine the toxicological aspects of consumer products which are ingested or applied on the body. No doubt that all the consumer products should be safe at levels of their intended use. However, safety should be defined in terms of acceptable risk or balance of risk, as there is no absolute safety or zero risk.[5] Or else many of the commonly used foods such as potatoes which contain solanine, cress which contains benzyl thioglucoside, mustard, cauliflower, tapioca etc. which contain goitrogenic substances, cabbage, charcoal grilled meat, spinach and kippers which contain small amounts of benzo(a)pyrene and cups of tea and coffee which contain caffeine would not have been allowed for human use.

Unlike drugs, which are prescribed to patients for a specific ailment, food or other consumer products are freely chosen with no limitation on intake or use. The consumer takes it for granted that government, health authorities and manufacturers have taken sufficient care to ensure fitness for human consumption. Quality of food items depend on composition which can vary with climate, soil condition, the type and strain of plant material, use of fertilizers, pesticides, harvesting practices, storage, etc.[6] Thus when the safety of food items are examined it should be viewed from the angle of nutritional quality, microbial and environmental contamination and chemical additives.

Thus the short- and long-term effects of the consumer products, including that of edible items, are of a varied nature. For example, the hazards from consumption of products made under poor hygienic conditions using contaminated water (microbes, amoebae, etc.) and scant attention paid to quality or chemistry of ingredients used; sold by vendors on the roadside, outside schools, seashore, railway platforms, bus stations etc., products such as *Bhelpuri,* Icecandies, *Sherbets, Jilebis,* sweetmeats tinted in different colours, *puri bhaji,* non-vegetarian and fried foods prepared using oils of questionable quality are too potent to be wished away and too complex for offering scientific solutions. Thus it would be an impossible task to deal with all such aspects at one time. Some of the well known effects such as cancer due to long-term usage of consumer products are reviewed.

2. CARCINOGENICITY

The diagnosis of cancer is an extremely traumatic communication for a person to receive; it marks a watershed between happiness (or its pursuit) and gloom, signifying the end of the world so far as that individual and his or her family is concerned. The purposeful search for carcinogens, and attempts to protect populations through legislation which often displays an over-reaction by regulatory agencies, therefore seems justifiable.

Carcinogens are categorised as either (i) genotoxic compounds which react covalently with DNA resulting in somatic cell mutation, which may or may not lead to a neoplastic cell depending on the activity of the repair enzymes or (ii) epigenetic or non-genetic compounds acting by mechanisms other than interaction with DNA and yet resulting in a mutational event. Another two-step theory postulates a double mutation of one or two regulatory genes which may be promoted by physical or chemical epigenetic stimuli.[7] Recurrent cytotoxicity is another epigenetic mechanism of carcinogenesis, the simplest example being the production of sarcomas following repeated subcutaneous injections of saline or glucose which, although themselves non-reactive, result in inflammation, necrosis and cellular division, and ultimately in a transformed or neoplastic cell.[7]

None of these hypotheses lead to a satisfactory or clear-cut understanding, and cancer is currently looked upon as a term for diverse diseases caused by chemicals or viruses or radiation or chronic mechanical irritation. The aetiology is said to be multifactorial and whether a dietary factor will lead to cancer or not is to a large extent dependent and governed by the air one breathes (carbon, asbestos etc.) the type of water (chlorine, pathogens, hepatitis virus, etc.) or beverage one drinks (coffee, alcohol) and how much tobacco (and betel) is chewed or smoked.

2.1 Screening Carcinogens

Feeding high levels of the test compound to various animal species throughout their life-span, or long-term skin-painting studies are cumbersome, time-consuming and expensive, and involve highly skilled personnel. Simple bacterial test systems which are very rapid, inexpensive and among the simplest to conduct have been developed.[8,9] In the widely-used Ames test [10], which takes about 3 days to complete, various strains of mutated *Salmonella typhimurium* (TA 1535, TA 1537, TA 1538, TA 98, TA 100 etc.) bacteria, specially prepared to be histidine-requiring and incorporating antibiotic resistance (TA 98, TA 100) and permeability factors, in the presence of the test compound with or without a metabolic activating mammalian microsomal enzyme preparation (S-9), will revert to non-histidine-requiring prototrophs if the test compound is a mutagen. Other *in vitro* bacterial assays are based on the principle of DNA repair or induction of lysogenic bacteria, and several *in vitro* tests use mammalian cell systems to identify mutagenic chemicals which might also have carcinogenic potential.

One plan suggests sequential steps for evaluation[11]: (a) chemical composition, metabolism and structure-activity information; (b) short-term *in vitro* tests: if these

are negative, further testing will depend on potential human exposure and any doubts one might have on the basis of chemical structure or physiological properties (e.g. hormones); (c) if positive, limited *in vivo* bioassays such as tumour induction in sensitive strains, which would yield results in 6 to 12 months; definite positive results in these *in vitro* and *in vivo* tests to be followed by; (d) chronic bioassay, to confirm questionable results in the more limited earlier testing, and for compounds that are negative in the preceding stages of testing but to which extensive human exposure is likely. Positive results in the *in vitro* and *in vivo* carcinogenicity tests suggests a genotoxic carcinogen, while carcinogenicity in animal bioassays but not in *in vitro* tests suggests an epigenetic carcinogen.

2.2 Natural Carcinogens in Foods

Beryllium, cadmium, chromium, cobalt, iron, lead, nickel, selenium, titanium and zinc salts have all been shown to be carcinogenic in experimental animals by different routes of administration.[7] There is also very strong epidemiological evidence that nickel carbonyl can cause lung and nasal sinus cancers among nickel refinery workers. However, there is little experimental evidence that metallic constituents of food constitute carcinogenic hazards in man. Selenium and lead are the only two elements which at high levels in the diet have been shown to produce experimental carcinogenesis in rats.

Among the naturally-occurring carcinogenic organic chemical compounds present in foodstuffs are pyrrolizidine and some other alkaloids present in higher plants such as Senecio, Crotalaria, Heliotropium, Veratrum, etc., the glucoside cycasin, present in the starch-rich fruit of cycads, a gymnosperm; bracken toxins present in ferns; and the mycotoxins produced by fungi, of which aflatoxins and sterigmatocystin are classic examples.[7] These toxic materials could produce cancerous tumours in livestock which might feed on the leaves of fodder plants containing them. The hazard to man through consumption of milk which might carry a carcinogen, or through contaminated meat, must be considered. Similarly the consumption of tubers, roots, fruits (cycad) or nuts (groundnuts) containing chemical carcinogens must be viewed with concern. Some colours used in foods (For example, Butter Yellow), has been shown to be a hepatocarcinogen.[12] Similarly, oil of calamus (obtained from the rhizome of *Acorus calamus)*, which has been used as a flavouring additive in foods and beverages, has been shown to induce malignant tumour in the duodenal region of rats that had received 500 to 5,000 ppm in their diet for more than 59 weeks. Eugenol and other constituents of spices with chemical similarities to safrole need to be investigated for their carcinogenic potential. There is no proof yet that chillies or their active principle capsaicin have any carcinogenic potential.

Smoking of foods as a means of preservation, or broiling as part of cooking, might generate polycyclic hydrocarbons which are a well-known class of chemical carcinogens.[7]

Another preservative, nitrate or nitrite (which might also naturally be present in foods) can act on amines in the gut with the production of nitrosamines and

nitrosamides which are strongly incriminated as potent agents responsible for the production of various cancers.[7] Pesticide residues in foods such as organophosphorus compounds or chlorinated hydrocarbons such as DDT must be viewed with concern, especially since accumulation of the latter in body tissues is well known. Various contaminants and adulterants in food such as ergot, datura, argemone, metallic colours, etc. also need to be properly investigated from the angle of their carcinogenic potential.

On the basis of epidemiological studies, the higher incidence of cancer of the colon and rectum in western societies has been related to diets which slow down intestinal transit time and produce small, firm stools.[7] Such diets also alter the faecal bacterial flora so that they contain a higher amount of anaerobic organisms of the bacteroides group, which are believed to convert bile acid cholate to potentially carcinogenic deoxycholate. These effects are attributed to a low level of fibre in the western diets, and dietary fibre could therefore be said to have an anticancer role in diet.

An increased incidence of colon cancer has also been recorded amongst Japanese migrants to Hawaii and California, and a positive relationship between colon cancer and consumption of beef has been shown among them.[13] Since beef is a major source of saturated fat in the United States, an association of colon cancer with dietary animal fat or cholesterol has also been propounded. On the other hand, a controlled clinical trial conducted in Los Angeles among 846 veterans fed either a conventional diet, or a diet containing four times the normal poly-unsaturated fat content at the expense of saturated fat and cholesterol, showed that the former diet predisposed to fatal atherosclerosis and the latter to fatal cancer. However, clinical trials of a similar nature performed in Oslo, London and Helsinki failed to confirm this observation.

The high incidence of stomach cancer in Japan was formerly attributed to a diet high in salted foods, low in milk, or containing polycyclic aromatic hydrocarbons from smoked fish. More recently it has been attributed to asbestos from the talc used on food processing machinery, which then found its way into contaminated rice. In Guam, parts of India (Orissa, Madras), Indochina, Indonesia and East Africa, cycad nuts are split into two, to yield starch which is used in food preparations. The toxic cycasin is often not completely removed, and is converted into the aglycone methyl azoxy methanol by the beta-glucosidase activity of intestinal microflora. This compound has hepatocarcinogenic activity, and a correlation has been reported between this latter condition and cycad starch intake.

Vitamin C, Vitamin E[14,15] and antioxidants have the ability to mop up free redicals by transferring a hydrogen atom or an electron, thus exhibiting protective action against carcinogenesis. Vitamin A also exhibits a protective action against cancer production,[16] in animal experiments, tumorigenesis is enhanced when the diets lack or are deficient in this vitamin.

Aflatoxin is one of the most potent carcinogens known,[17,18] and has been shown to produce cancer in a very large number of species of laboratory and farm animals. Yet there is only tentative evidence that human consumption of food contaminated with aflatoxins might cause liver cancers in man. This is being stated to emphasise

that chemicals indicted as carcinogens tend to get so branded through repetitive mention in scientific and review papers and text books, and indeed there are a large number of ifs and buts before they can really produce carcinogenic activity in human beings.

Then again the quantitative risk for safrole (active at 2000 ppm) and aflatoxin B1 (active at 1 ppb) cannot be the same, and yet the concept of 'zero tolerance' tends to club them together.

The Hindustan Lever Research Centre developed a pilot scale process for ammoniation of groundnut cake containing high levels of aflatoxin, whereby the latter drops to below 50 ppb (parts per billion) and such processed material was found to be without risk in subchronic toxicity studies in rats and poultry.

The prevention of manifestation of cancer due to carcinogens in food probably depends on the ability of the body to de-activate the proximate carcinogens and prevent the formation of the ultimate carcinogens, i.e. to have detoxifying mechanisms which will outpace the mechanisms of activation of chemicals into reactive groups.[19-21] Having efficient DNA-rapair mechanisms and proficient immunologic surveillance are also of paramount importance.

2.3 Dyes

Hair dyes were used without appreciation about their risk until a few years ago, when the main ingredient of such dyes viz. p-phenylene diamine already known as a contact allergy producing chemicals,[22] was suspected to be a carcinogen because it gave a positive result in the Ames test. Many other dyes particularly "aniline" dyes are known to produce papilloma/carcinoma of bladder.[23] Some dyes such as 2-naphthylamine are known to produce urinary bladder cancers in human beings and dogs but not in other laboratory animals. This is attributed to metabolic activation by N-hydroxylation which occurs in man/dog but not in the animals in which the compound is detoxified by ring hydroxylation.[24] Tetra-azo dyes and benzidine based dyes are well known carcinogens, so are N-nitroso compounds or nitrosating agents. Thus there is need for every precaution to be taken in the choice of the colourant used in foods or cosmetic products so that risk to the consumer is avoided.

On the other hand, ultra-violet (U-V) radiation from the sun is particularly harmful in white skinned people and is known to produce skin cancers. Melanin screens the U-V rays and protects dark skinned people in whom skin cancers are rare. The use of cosmetics containing sunscreen chemicals such as cinnamic acid and benzophenone derivatives can provide protection against U-V induced skin cancers.

3. SYSTEMIC HAZARDS OF CONSUMER PRODUCTS

3.1 Edible Oils & Fats

The consumption of high level (more than 30 per cent) of fats in diet, particularly rich in saturated fats and cholesterol is recognised as an important factor in the

causation of atherosclerosis and its sequelae such as myocardial infraction or cerebral stroke.

Vegetable oils such as those of mustard/rapeseed which are rich in erucic acid (22:1 C) have been shown to accumulate in the heart in acute experiments in laboratory animals giving rise to pale hearts in rats and hydropericardium in ducklings, and continued feeding has been shown to be associated with myocardial fibrosis.[25-27] However, this latter phenomenon has been observed in animals fed nil erucic oils or fish oils containing polyenoic acids.[28] Such changes in an important organ like the heart, surprisingly have not been associated with decreased life span in experimental animals. Postmortems (human) carried out in predominantly mustard oil consuming parts of India such as West Bengal also failed to reveal any correlation between high levels of mustard oil consumption and myocardial involvement. Even so, the Council of Europe has stipulated a maximum level of 5 per cent erucic acid in vegetable oil products.[29] The Indian regulatory agencies, basing their judgement on prolonged epidemiological experience and, perhaps rightly so, have not fallen in line with the Council of Europe legislation.

Seeds of *Argemone mexicana* a thorny shrub with yellow flowers growing by the roadside in many parts of India, resemble mustard seeds in appearance, and deliberate adulteration of mustard seeds is possible. Argemone oil contains the alkaloids sanguinarine and hydroxy sanguinarine and these are reported to produce inflammatory changes in blood capillaries leading to dropsy.[30] Many instances of epidemic dropsy have been attributed to consumption of edible oils containing high levels of argemone oil.

In 1981-1982, several hundred people died in Spain due to consumption of edible oil[31] which was contaminated (probably with triorthocresyl phosphate). The people suffered from an initial arteritis and passed on to a chronic phase with severe painful and distressing muscle weakness.

3.2 Protein Foods

Among the proteinaceous foods the commonest hazard is allergy. Allergy to milk proteins, eggs, prawns or bengal gram, etc. are quite well known and can produce, if the consumer is not watchful, serious consequences like collapse with drastic fall in blood pressure, apart from the usual signs of hives, itching, stomachache, and other manifestations of an anaphylactic reaction.

Soybean, contains antitryptic factors[32] and if fed unprocessed to animals over extended periods can produce pancreatic exocrine cell tumours. These are probably a consequence of prolonged overstimulation of pancreatic exocrine cells to produce digestive enzymes in response to protease inhibition in the gut and are not really due to any unknown toxic factor.

During preparation of soya isolates and concentrates, the soya flour is heat/alkali treated to get rid of the trypsin inhibitor. However, the formation of a novel amino acid lysino-alanine[33-35] which can produce cyto and karyomegaly[36] (increase in size of

cells and nuclei) of kidney tubules, has to be borne in mind, so that the processing conditions adopted are properly regulated and are not too drastic.

The use of kesari dal (*Lathyrus sativus*) as a component of food is banned under the PFA Act 1954 and yet sporadic cases of lathyrism occur due to consumption of this dal in food over extended periods of time. Two types viz. Neurolathyrism and Osteolathyrism due to the chemicals oxalyl-diamino propionic acid[37] and beta-aminopropionitrile[38] present in kesari dal, have been identified. These can produce pathetic incapacitation. Greater awareness and research inputs in breeding varieties lacking the chemicals will help root out this disorder. Lathyrism also highlights the toxic potential of unusual amino acids.

3.3 Metals

Severe neurological disorders also occur in mercury poisoning as occurred in the Minamata bay tragedy in Japan where people had consumed fish contaminated by mercury from industrial, waste.[39] Even more extensive damage resulted from contamination of bread made from cereal grains treated with alkyl-mercury fungicides.[39] In 1971-72 such an episode occurred in Iraq involving 6,000 cases and 500 deaths.[39]

Cadmium is another metal which can be present in excessive amounts in food. While usual concentration in foods is less than 0.1 μg/g, net weight, excessively high concentrations, sometimes exceeding 10 μg/g, can occur in shellfish, liver and kidney. Afflicted people generally suffer from severe rheumatic, myalgic and bone pains. Such a mysterious disease was first identified in Japan and was called 'Itai-Itai' and was due to consumption of rice having high cadmium content from the rice fields receiving effluent from a lead-zinc-cadmium mine upstream from the rice fields.[40]

Manganese is another metal present in all living organisms, its principal intake is derived from food. Vegetables, germinal portion of grains, fruits, nuts, tea and some spices are rich in manganese. Chronic manganese poisoning produces a Parkinson disease like syndrome with mask-like face, difficulty in walking with retropulsion or propulsion,[41] difficulty in speech and compulsive behaviour all related to an encephalopathy caused by selective damage of subthalamic nucleus and pallidum by manganese.

In India, in some pockets high fluoride levels in water have been identified and people with genu valgum (knock knee) found in nearby locations e.g. some villages of Andhra Pradesh.[42] Unfortunately, these cases are not adequately researched and very often categorised as victims of fluorosis, while there are others who have attributed the conditions to high levels of molybdenum and low levels of copper in the diet of these villagers.[43]

3.4 Non-Metallic Substances (Fluoride)

The use of fluoride in reducing the incidence of dental caries is now well established as a non-controversial scientific fact.[44,45] Fluoridation of water as a public health

measure is widely practised in many parts of Europe and USA. Dental Associations and experts in the WHO have advocated toothbrushing with effective fluoride toothpastes to be included as an integral component of public health programmes to improve oral healths.[46] Fluoride converts hydroxyapatite present in teeth enamel into fluoroapatite thus strengthening the teeth, thus offering greater resistance to carious damage or cavity formation in teeth caused by organic acids produced by fermentation of sugars.

It is estimated that approximately 1 mg of fluoride may be the intake from food, water, milk and tea (which is particularly rich in fluorides). Water fluoridation programmes aim at providing 1 mg of fluoride intake per day. A total intake of 3 mg/day of fluoride is unassociated with any adverse effect. At 4 mg/day intake the teeth show white specks and are said to present a 'mottled' appearance.[47]At higher levels of 5 to 6 mg/day the discoloration of the teeth is said to be brownish. These are cosmetically unacceptable effects but not health hazards. However, for crippling fluorosis to occur it is reported that intakes of fluoride, more than 20 mg/day for many (11-20) years must happen, the sort of exposures which occur in industrial situations such as quarrying/mining of fluorides. But this is also manifested as 'poker back' or hardening of bones rather than weakening leading to 'genu valgum'.

There is no evidence that fluoride in toothpaste can cause any harmful effects. The general level of fluoride is never more than 1500 parts per million i.e. less than 1 mg of fluoride is available per brushing. The amount of fluoride intake due to swallowed toothpaste even in small children is no more than 0.5 mg/day or at the most 0.8 mg on some days. Even these values are really exaggerated to err on the side of safety.

Fluoride is an essential nutrient. Much of the ingested fluoride is excreted in urine and small amounts is stored in teeth and bone. Apart from the beneficial activity in prevention of caries, fluorides are being used for prevention and treatment of Paget's disease and old age osteoporosis.

3.5 Other Substances

The use of chloroform in toothpaste or other consumer products is banned because of its carcinogenic potential.[48] While cinnamon and clove are commonly used spices, some individuals are allergic to them and therefore the use of their active principles like cinnamic aldehyde, eugenol/isoeugenol in flavours is generally avoided.

Among the food additives monosodium glutamate, meat flavour enhancer, has received much attention being responsible for the stomach upset called 'Chinese restaurant syndrome'. But more importantly based on brain lesions produced in suckling mice,[49] its use in infant foods is not advocated.[50,51]

Feingold[52] has held that all food additives produce hyper kinesias and learning disorders in children and has been a strong proponent of bland diet therapy. However, his observations have not received wide support.

Among the germicides, hexachlorophene has received much adverse publicity for causing brain damage as a systemic effect. When one wants to incorporate

physiologically active material in cosmetics and toiletry products, their safety in use in terms of systemic effect due to percutaneous absorption needs to be ascertained. Using radio labelled chemicals it is possible to know about the kinetics of how much and how far the chemicals can pass through the skin. But from the risk angle, generally the material is applied to the skin of rabbits repeatedly and depending on the type of usage of product, say at the end of 21 days or 90 days or 1 year, a detailed examination of blood and vital organs is carried out for an assessment of safety. Such a test has also the advantage of yielding information on the local effect produced on skin due to repeated application.

4. LOCAL EFFECTS ON SKIN

4.1 Allergic Contact Dermatitis

This condition results from contact with substances to which skin has been sensitized by previous exposures which did not produce any toxic effect. Substances vary in their ability to induce sensitization and the risk of sensitization depends on individual susceptibility which cannot be predicted.

The allergic eczema can cause intense discomfort. The repeated healing and breakdown of skin tissue associated with itching, scratching can lead to a disabling skin eruption of a long lasting character which can result into tension ranging from mere annoyance to rage to despair and sometimes even result in serious nervous overtones. This hypersensitivity may last for a long time, say more than 2 years.[53] It is, therefore, of paramount importance to make sure that skin products do not contain sensitizer, more so when these are intended for use on infants and small children. When an organism is confronted with a foreign protein (antigen) it has the capability of producing specific protein called antibodies or inducing changes in cells called T lymphocytes (and to a lesser extent in other cells called basophils and macrophages) with which antigens can specifically react. The production of such reaction when it occurs, cause breakdown of cells and manifest the clinical condition referred to as allergy.

The antibody mediated or immediate type of reactions include anaphylaxis, asthma, urticaria and other types of responses called type I to type III reactions, whereas contact allergy is considered to be due to a cell mediated or delayed type reaction[54] (type IV).

In contact allergy (type IV) a small molecular weight chemical which is a sensitizer (termed hapten) can penetrate into the skin (from a skin product) and form a covalent bond with protein. The capacity to induce contact sensitization is, therefore, proportional to the solubility of chemical in fat and its reactivity with proteins. This protein hapten complex remains in the skin and must persist in the skin for a certain length of time. It then induces proliferation and other changes in lymphocytes (T-lymphocytes) in the lymph glands and such transformed lymphocytes are termed sensitized. These sensitized lymphocytes circulating in blood can elicit the allergy response when the specific hapten is applied to skin, usually in a non-irritating concentration. The resultant response is a local inflammatory reaction which reaches

its peak 24 - 28 hours after the challenge with the hapten, slowly disappearing over the next few days. The main features of this response are redness and a more or less pronounced thickened swelling (induration), some times with associated skin breakdown, microscopically it shows a cell infiltrate of mononuclear cells which are immobilized in the lesion.

The test procedures are so designed as to allow any of the chemicals, in the skin preparation to induce a state of sensitization in guineapigs by repeated intradermal injection[55] or by reducing the number of injection and shortening the period of induction by administering the suspect material in close proximity of the draining lymph node, or by inducing an enhanced state of constitutional reactivity by injecting the test substance along with complete Freund's adjuvant as in the Magnusson and Kligman method.[56] It is to be remembered that genetic make up, age, weight, etc. play an important role in allergic reactivity and therefore guineapigs chosen for such testing are treated with due attention paid to age, weight, sex and ensuring that guineapigs are bred from a stock which show positive reactivity to standard and well known contact allergens like DNCB (Dinitrochlorobenzene)

Despite following the stringent animal test requirements, it is possible to miss allergenic chemicals to be used in a cosmetic or toiletry product, and therefore, further patch testing procedure using 200 human volunteers have been recommended by Draize and modified by others to maximise the effectiveness of the procedure in order not to miss identifying a contact allergen.

Based on the ability of production (lymphokines) of activated or sensitized lymphocytes to inhibit migration of macrophages, *in vitro* techniques based on the logic of contact allergy reaction have been developed to supplement information obtained in the above mentioned whole animal experiments.

Chloro-sulphones present as an impurity in some detergent actives such as sodium lauryl ether sulphate (SLES), sodium alpha olefin sulphonate[57] and cinnamic aldehyde, isoeugenol, methyl heptine carbonate used as perfumery ingredients are known to be potent human contact allergens. p-phenylene diamine used in permanent hair colorants and formaldehyde used as preservative in cosmetics are also potent contact sensitizers but can be safely used by majority of people, who do not show an allergic response particularly if the level of usage in the consumer product is below the threshold sensitizing level.

Apart from substances which are initially responsible for provoking hypersensitivity, there are substances which elicit unfavourable responses when they come in contact with already sensitized skin. There are well authenticated cross-reactions between different antimicrobials, fragrant chemicals etc.[58] For example, some aspirin sensitive individuals are known to exhibit adverse responses when they come in contact with salicylates, benzoates,[59] etc.

4.2 Photo-allergic Dermatitis

In photo-allergy, light alters the structure of a chemical or its metabolite which then becomes a true allergen. After an incubation period, patients develop papules,

eczemation or urticarial lesion on exposed sites. Most clinical and laboratory studies related to allergic contact photo sensitivity, have been based on the original observation of Wilkinson[60] in 1961 that 3, 3', 4, 5, tetra chlorosalicylanilide (TCSA) which was used as an antibacterial agent in soaps, had a high photo-allergic potential in human beings. The other materials incriminated in having this type of action are some of the optical bleaches, bithional, other halogenated salicylanilides (TBS) and some drugs. 6 methyl coumarin and musk ambrette used in perfumes contained in cosmetics/toiletries have also been recognised as photoallergens. These were first identified as photoallergens in sunscreen products and after shave lotions respectively.

The chemicals which induce photo sensitization reaction[61] generally include di- and tricyclic resonating compounds that fluoresce and their absorption spectrum is in the ultraviolet range (290 - 350 nm) range. This could therefore be used as a preliminary screening procedure before chemicals are considered for animal tests. Obviously not all materials in these classes are sensitizers but generally photosensitizers are U-V absorbers. Guineapig is the animal of choice, and test procedure are essentially similar to the repeat application technique of Landsteiner and Chase except that in testing for photo-allergy the compounds are applied to the guineapig followed by irradiation successively with fluorescent 'Sun lamp' tubes (Westing House) emission (285 - 350 nm) and 'Black light' fluorescent tubes (Westing House, General Electric) emission (320 - 450 nm). The concentration of solution, target skin distance, time of irradiation (i.e. dose) etc. are best arrived at by using TCSA as a positive control in the development of this prediction technique, since reporting of false negatives due to faulty technique can be a pitfall.

4.3 Skin Irritation

Many chemicals coming in contact with skin can produce an irritant response which is manifested as redness, swelling, scaling, thickening of skin and in severe cases breakdown of skin layers or ulceration. It is a dose related response. Irritants which produce deep seated injury with dissolution of coagulated skin proteins are referred to as corrosives. Generally, highly alkaline or highly acidic materials produce irritant/corrosive effects. Fabric washing powders formulated to contain a very high proportion of soda ash, and having high pH, produce unduly irritant reaction on skin causing acanthosis and chronic dermatitis. The surfactant activity of the active detergent is more marked under high pH condition, where the protective 'acid mantle' of skin, no longer functions as barrier and can produce deep seated injury. It has become common practice among some producers of detergent products to reduce cost of the formulation by inordinate increase of alkali (soda ash) in the product, paying scant attention to the well-being of the consumer[62].

It is customary to test irritancy of products in laboratory animals by comparing them with marketed products, regarding which there is sufficient experience and database, which then can be used as indicators of threshold irritancy level; any response which is markedly greater than that, being deemed unacceptable for safety clearance and considered to pose a risk to the unsuspecting consumer. Irritancy testing can be carried out in a manner simulating use of the product and the guineapig immersion test provides reliable ranking of irritancy potential of various fabric washing products[63].

The covered patch test or Draize test and repeated application test in rabbits, rats or guineapigs can also be standardized for assessment of irritancy potential by macroscopic evaluation by trained assessor and can sometimes be coupled with histopathological evaluation for further increasing reliability and sensitivity.

Apart from chemical irritancy, Talc sometimes contains spores of *Clostridia tetani* and requires to be sterilized to prevent dermatitis and any problems of inhalation toxicity.

5. TERATOGENICITY

The thalidomide tragedy[64,65] resulted in approximately 10,000 malformed children in Germany, Japan and other parts of the world, due to consumption of drug by women during pregnancy, brought a new dimension to toxicology, viz. the hazard of chemical teratogens (i.e. compounds, the consumption of which during critical periods of pregnancy induce malformation in the baby). Although such an effect due to the topically applied products have so far not been highlighted; it would still be prudent to make sure that the products both edible as well as those meant for skin application, and particularly those sold OTC (over the counter) can be used with impunity by all consumers including pregnant women. Here it is well to remember that aspirin and vitamin A are well known animal teratogens. Similarly, toxic inorganic compounds of lead, mercury, molybdenum, manganese or organic compounds like N-nitroso compounds, nitrosomethyl benzenamide, nitrosomethylurea, aflatoxin etc. have demonstrable teratogenic activity as well. This information is useful although of no direct relevance in the area of consumer products. Teratogenicity induced by chemicals is also dependent on the host and often predictive testing is carried out in 2 or 3 different animal species.

6. HEALTH HAZARDS DUE TO PACKAGING MATERIALS, PLASTICS AND RUBBER PRODUCTS

Toxicological risk due to the packaging materials, plastics and rubber products have not generally been paid sufficient attention. While regulatory agencies often formulate specifications for packaging materials for edible items, ingestible substances, cosmetics and other consumer products, there is hardly any monitoring to ensure that manufacturers adhere to these specifications. The phenol smelling multicoloured (possibly even using carcinogenic non-edible dyes) plastic bottles meant for carrying drinking water by the school going children, the attractively coloured toys (again using dyes of questionable safety) which children often bite, nitrosamine containing feeding bottles, rubber teats, plastic containers made out of recycled plastics to hold and store edible items such as fatty foods, milk products etc. can pose a real danger to health in the long run, and therefore, it is essential that safety conscious manufacturers and regulatory agencies ensure that risk to health of consumer through ignorance, wilful neglect or malfeasance, will be eliminated.

7. RAW MATERIAL PURITY

This brings us to the very important subject of raw materials and chemicals used in formulating consumer products. For example, what is called paraffin wax many

contain many impurities with the result that some batches would cause skin sensitization and others not. Therefore, prior to embarking on expensive safety testing using animal models, stringent chemical/physical specification ought to be drawn for the raw materials and the mode of processing of the final product. If there is a change in the raw materials to be used or a change of supplier or alterations in the processing, this would warrant, if not large scale animal experimentation at least 'considered thought' from the safety angle. Fragrance materials such as balsam of Peru, terpenes, essential oils, colourants, plastic raw materials, various additives used are of particular relevance in this context.

8. CONCLUSION

The unsupervised nature and repeated and long-term use of consumer products involving a wide spectrum of user groups such as infants, children, adults, pregnant women, aged, sick and convalescent make it essential that such usage will not adversely affect health in the long run. Unfortunately, many effects are generally too subtle to begin with and one is totally unaware of their latent presence until thay have progressed to such an extent that well-being is significantly hampered (e.g. neurotoxicity, sensitization, malformation, etc) and sometimes, life itself is threatened as in the case of cancer. But even at that stage it may not be possible to take immediate remedial measures as one is not sure of the causative culprit, unlike in the case of medically administered drugs. Hence it is all the more important that the manufacturers of consumer products discharge their social responsibility by ensuring that their products are safe during continued use. This could be achieved by resorting to the use of chemically well defined and biologically acceptable raw materials, and use of well known process conditions and where the safety of the product is already established. Biological testing is particularly important when one intends to use a new ingredient or a new process.

Even so, the final judgement on safety should be based on a critical appraisal of biological responses, pattern of usage (acceptable daily intake) and judicious logic; so that it will not harm inventions, innovativeness, business or health of the user.

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