PERCUTANEOUS ABSORPTION AND CHEMICAL CARCINOGENESIS

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Chemical agents which are carcinogenic may enter the animal organism through three possible routes: the skin, respiratory tract and the gastro-intestinal tract. In this thesis, we shall consider the percutaneous transfer of chemical agents which may induce cancer in the skin as well as other organ systems of man and experimental animals.

First let us consider the role of the skin in relation to the human environment. We recognize the skin as an:

1. Important interface between man and his environment.
2. As an organ of defense and adaptation.
3. As a portal of entry for chemical and biologic agents.
4. As a susceptible target organ for toxic agents, even when absorbed through other routes.
5. It is a uniquely accessible model system for studying a variety of important biologic phenomena including carcinogenesis.

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Adaptive and Defense Mechanisms

I shall not attempt to describe in any detail in this presentation the adaptive and defensive mechanisms of the skin. I shall simply list these mechanisms since they represent important biologic characteristics of that organ system in which the carcinogenic process may occur:

1. The epidermal barrier: It is comprised of an 8 to 15 cell layer thick, non-living structure which offers a measure of resistance, although imperfect, against penetration of chemical carcinogens as well as ultraviolet light. It prevents water and solute loss from the body.
2. The presence of melanin pigment in the skin prevents ultraviolet damage. It is a deterrent to the carcinogenic effects of ultraviolet radiation which may act in combination with chemical agents. It is both a physical and chemical screen.
3. The immunologic responses, particularly the "T" cell system, provide biochemical as well as cellular defenses against the absorbed chemical agent. If tumor cells are produced, immunologic defenses inhibit the multiplication and growth of these abnormal cells.

Those defenses not directly related to chemical carcinogenesis in the skin include:

4. Thermal regulation which involves physiologic activity of the blood vessels and the eccrine sweat gland secretion.
5. Dermal resiliency offered by elastic and collagen fibers.
6. The bacteriostatic and fungistatic property of sebaceous and epidermal lipids.
7. Sensory nerve endings in the skin provide a mechanism for transmitting information about state of the environment and its noxious stimuli.

Routes of Percutaneous Absorption:

There are four possible routes of penetration:

1. The trans-epidermal route in which the material is transferred through the epidermal barrier.
2. The pilosebaceous route: the hair follicle and sebaceous gland.
3. The eccrine sweat gland and its duct.
4. The apocrine glands associated with follicular appendages.

In the case of the eccrine and apocrine sweat glands, the scientific documentation for those structures acting as a frequent route of penetration is very meager.

The pilosebaceous route is regarded as the shunt or transient-state portal for most substances which penetrate readily. The epidermal barrier is regarded as the steady state portal. It takes time for the barrier to become saturated with the penetrant, and when it does, there is a constant and steady transfer of penetrant from outside of the skin into the living epidermis, and subsequently the dermis, where it may be absorbed into the circulation.

Mechanisms of Transfer

Percutaneous absorption is a passive transport process. Because of its cellular and biochemical characteristics, the normal skin offers the best protection against:

1. Compounds of high molecular weight.
2. Electrolytes.
3. Strong polar non-electrolytes.

It offers the least protection against low molecular weight compounds which are non-electrolytes, and especially those which have high lipid solubility. These

characteristics can be simply expressed in a mathematical formula known as Fick's equation:

$$J_S = \frac{Km\ Dm}{\delta} \cdot \Delta C_S$$

This equation describes passive transport across the stratum corneum.

J_S - represents the flux or amount of material moving across the unit area of stratum corneum in a unit time. It is directly proportional to K_m - the partition coefficient (lipid/water) which is the tendency of the solute to leave its vehicle from the outside of the skin and enter the stratum corneum. It is also directly proportional to the diffusion constant or D_m which is a measure of the ease of movement across the stratum corneum, and it is also directly proportional to the difference in the concentration across the stratum corneum represented by ΔC_S. The flux is inversely proportional to the membrane thickness which is represented by δ .

Further, the partition coefficient K_m, is a measure of the penetrant's solubility in the stratum corneum as compared to the solubility in the vehicle outside the skin. This value can be determined experimentally. In general, K_m is higher for non-polar compounds (lipid soluble compounds) than for polar compounds (water soluble compounds). Further, the more polar groups such as

OH, COOH, NH_2, there are in the diffusing molecule, the lower the diffusion constant.

Difference in concentration across the stratum corneum, ΔC_S, is nearly equivalent to the concentration in the presenting solutions since there is a rapid diffusion from the internal surface of the stratum corneum through the viable epidermis; and, therefore, the concentration at the internal surface of the stratum corneum is approximately zero at all times. The skin, therefore, offers the best protection against water soluble substances which have multiple polar groups, and least protection against lipid soluble materials which are presented to the skin in a polar vehicle. Protection against lipid soluble materials is increased if they are presented in a non-polar vehicle.

If one examines the types of agents which are carcinogenic to mammalian, including human skin, it is somewhat obvious that most of the substances such as polycyclic aromatic hydrocarbons are non-polar compounds with high lipid solubility. This is not the case for inorganic arsenical compounds where the major route to the skin is the gastrointestinal tract, not the skin.

Factors which are known to increase the rate of penetration or enhance absorption are:

1. Physical or chemical damage to the barrier, especially disruption.

2. Hydration of the barrier.

3. Increasing environmental and/or tissue temperature.

4. Increasing concentration of the penetrant.

5. Location on body surface. There is a 100-fold difference in flux between palmar and scrotal skin.

6. Reservoir capabilities.

7. Rate of blood flow in the dermis.

8. Chemical factors such as molecular size, concentration of solute, lipid solubility, state of ionization, pH and biotransformation mechanisms.

Consequences of Percutaneous Absorption

What are the consequences of absorption as related to toxicity and/or carcinogenesis? The penetrant going through the skin, may have little effect on the skin but produces injury in some other organ system e.g. liver, kidney, brain, etc. Or the penetrant may affect the skin as well as a remote organ system. The penetrant may affect the skin with no apparent effect on any other organ. Or there may be neither injury to the skin or any remote organ.

Physical Factors in Carcinogenesis

Before we discuss chemical carcinogenesis in human skin, it is necessary to bear in mind that the most common and constant carcinogenic agent for the skin of man is actinic ultraviolet radiation. In this connection, it has been shown epidemiologically, that the non-melanoma skin cancer rate in white population at the latitude of the state of Texas is four times that of populations living at the latitude of New York City or Detroit. The rough comparison is 120 cases per hundred thousand population in contrast to 30 cases per hundred thousand population. The frequency of non-melanoma skin cancer in non-white populations such as blacks, is approximately 2 to 4 cases per hundred thousand. There is little difference between the frequency among non-whites in the southern sections of the United States as compared to the northern part of the United States. The critical factors are wave lengths of solar radiation, intensity of radiation, duration, numbers of exposures and amount of melanin pigment. Dose is related to occupation and/or life style. The most important genetic factor is melanin pigment. In order to differentiate the chemical origins of cancer from physical sources, we must be alert to the uses of and exposure to ionizing radiation whether

it be accidental, occupational, or therapeutic. The consequences of these are well-known. Among other physical factors, of course, trauma and burns must be taken into consideration.

Chemical Factors in Carcinogenesis

Historically, the chemical carcinogens have been identified in several major sources: the extraction, refining and the utilization of fossil fuels such as coal, petroleum, and oil shale, and metals such as arsenic. The first description in the 18th century by the surgeon, Percival Potts, of cancer of the scrotum among chimney sweeps involving soot, is well-known to all of you. Since the 18th century, many observations have been made on the cause-effect relationship between fossil fuel uses and skin and lung cancer. These involved workmen in the coal-tar industries, gas plants, petroleum, and shale oil refineries as well as in spinning equipment operators in textile industries and in machine shops using lubricating oils which contain polycyclic aromatic hydrocarbons or polynuclear aromatic agents (PNA's). The same types of exposure which result in skin cancer from the percutaneous absorption of polycyclic aromatic hydrocarbons such as benzo (a) pyrene, causes lung cancer by inhalation. This has been observed in the coal-tar industry, in gas plants, and among coke oven workers.

There is now good reason to believe that the polynuclear aromatic compound alone is not likely to induce lung cancer readily, but that agents which promote epoxidation of the PNA's, such as particulates and sulfur oxides, are important factors. Other promoting agents such as long chain alkyl compounds, phorbol esters, etc., have been shown clearly to enhance skin cancer in experimental animals. However, the identification of promoting agents in man and their role in skin or lung cancer has been made only by inference from the animal studies.

Arsenic as a cause of skin and lung cancer has been observed in mining and refining of arsenic ore and in the manufacture of arsenical compounds for a variety of uses. Keratoses and skin cancer have been known for many years to be induced by the therapeutic use of potassium arsenite contained in Fowlers' solution. However, there are differences in the response of exposed populations. Workers exposed to the manufacture of lead arsenite and calcium arsenite have a higher death rate from respiratory cancer than expected (3.45:1). No observations, however, were made about the frequency of skin cancer in this group. In a population exposed to arsenic trioxide and arsenic acid the standard mortality ratio (SMR) was 17.24 for respiratory cancer. In this group of

decedents, no skin cancer data were revealed. More recently, carcinogenic properties have been demonstrated for and associated with the exposure to plastic monomers, nitrosamines, coloring agents or dyes, and a variety of industrial chemicals.

Mechanism of Carcinogenesis

Although it will not be possible to discuss the mechanisms of carcinogenesis in detail, biologically, carcinogenesis is regarded as a 2-stage process in which chemicals which are electrophilic reactants combine covalently with nucleophiles in DNA's, RNA's, and proteins. Although the critical cellular target of mutagens is DNA, the cellular targets of carcinogens have not been defined.

In the first stage, the initiator alters DNA of the target cell. In the second stage the promoter activates genes causing the genotype of tumor cell to divide and multiply. There are complex immunological and hormonal restraints which must be overcome as well.

Biotransformation Systems Involved in Carcinogenesis

When an agent is absorbed percutaneously, any systemic toxicity that occurs should be the same as that which would occur following exposure to the chemical by any other route, e.g., gastrointestinal tract or by inhalation, unless the skin specifically confers some specific toxic property to the compound. There are basically two considerations which contribute to the rise or fall of concentration of the agent or its metabolite in the bloodstream which is related to

the concentration available to the receptors for each chemical agent. These factors are those which affect absorption through the barrier, such as damage to the barrier, hydration, concentration of the area of the skin penetration, etc., and biotransformation.

Let us consider some of the known biotransformation mechanisms in mammalian skin. We know the liver to be an important organ of biotransformation. The skin, however, is able to metabolize only about 2% by unit weight of tissue as compared to the liver. Since the skin is about three times the weight of the liver in man, it is also an important organ of metabolism of absorbed compounds. When chemicals are absorbed through the skin they may be biotransformed into less toxic or more toxic compounds. The biotransformation systems in the skin include: oxidation, reduction, hydrolytic and conjugative reactions. For example, 17 β -estradiol is converted in the skin to estrone, and hydrocortisone is converted into cortisone.

It has been demonstrated that chemical carcinogens bind to skin constituents. For example β-propiolactone when applied to mouse skin binds covalently to skin DNA and the degree of binding to skin DNA varies directly with the susceptibility of the mouse species to tumor formation. The enzyme system for the

generation of reactive metabolites involved in binding of PAH to DNA is the mixed function oxidase system. Aryl hydrocarbon hydroxylase (AHH) is a class of enzymes involved in liver and skin metabolism of PAH carcinogens. It is a mixed function oxidase requiring NADPH and O_2 for optimum catalytic activity. It is found in the microsomal fraction of the endoplasmic reticulum.

It is now believed that the three enzymes: AHH, epoxide hydrase (a microsomal enzyme that cleaves arene oxides into dihydrodiols which are metabolized by AHH into diol-epoxides) and glutathione-s-epoxide transferase, a cytosolic enzyme, are all essential for the metabolism of polycylic aromatic hydrocarbon carcinogens. Tumor susceptibility of a particular species is probably dependent on the relative activities of these enzymes in skin.

There is now additional evidence of the role of cutaneous metabolism in tumor promotion. When TPA or 12-o-tetra-decanoylphorbol-13-acetate is used as a promoting agent for skin tumor development with 7,12-DMBA (dimethylbenz(a) anthracene), the promotion is uniformly associated with the increase in activity of ornithine decarboxylase (ODC) with the resulting increase in skin putrescine. Non-promoting hyperplastic agents do not raise the ODC level. When ultraviolet light (UVB) is added to that system, there is a dramatic increase in epidermal

ODC and s-adenosyl-L-methionine decarboxylase (AMD) activities of hairless mice before an increase in epidermal DNA synthesis occurs. The induced ODC activity and rise in putrescine level can be supressed with vitamin A (13-cis retinoic acid), and other retinoids. Whether promoting agents other than TPA are accompanied by the same increase in ODC and putrescine has not been determined. Unfortunately, there is a limited amount of information about the rates of absorption or flux of either PAH's or other known carcinogens in human skin. There is better information regarding penetration of nitrosoamines, hydrazine, plastic monomers, chromium compounds, aromatic amines, and some of the regulated industrial carcinogens.

METAL CARCINOGENS

1. Arsenic

It has been known for some time from clinical and epidemiologic experience that large numbers of skin cancer cases have been reported among those exposed to inorganic arsenic through drugs such as Fowlers' solution, arsenic in drinking water, or arsenicals manufactured and used as pesticides. In all of those cases there is little documentation for the skin as a route of absorption. The gastrointestinal tract, and possibly the respiratory tract, is the route

of absorption. In workers involved in manufacturing arsenical pesticides there is an excess of mortality for respiratory cancer as was indicated in an earlier section of this paper. Four cases of human hemangiosarcoma of the liver have been reported due to medicinal arsenic and one from general environmental exposure. Case-control and cohort studies in copper smelters demonstrated a significantly increased mortality from respiratory cancer among the workers. A similar increase in respiratory cancer is found among people living in the neighborhood of copper and lead smelters where arsenic is emitted.

There is inadequate evidence that arsenic compounds are carcinogenic in experimental animals. It has not been possible to induce and/or promote either skin or respiratory cancer when substances such as potassium or sodium arsenite are applied to mouse skin, nor will the administration of sodium arsenite intratracheally or by inhalation induce pulmonary tumors in mice, nor will arsenic trioxide induce tumors in rats. There is inadequate evidence for arsenic as a carcinogen in experimental animals but very adequate documentation of inorganic arsenic as a carcinogen for the skin and the lungs in man.

2. Chromium

There is considerable evidence which demonstrates that Cr VI is absorbed through the skin and transformed into trivalent chromium. Chromic acid and

the dichromates are both irritants and sensitizers to human skin. Hexavalent chromium is reduced to trivalent chromium in the skin chiefly by HS groups in amino acids. These conjugate with proteins to form a full antigen. Nevertheless, neither Cr VI and Cr III are carcinogenic for human skin. From epidemiologic and clinical information on workers in chromate production there is a high risk for lung cancer among workers where dichromates and chromium trioxide are processed. Two studies of the chromate pigment industry, especially where lead chromate is made, suggest a substantially increased risk for lung cancer. It would appear that the carcinogenic compounds for the lungs are calcium chromate, lead chromate, strontium chromate, chromium trioxide and and zinc chromate in rat. These are all relatively insoluble chromium compounds.

BERYLLIUM

While it is known that beryllium compounds will penetrate the skin and cause irritant and/or allergic reactions in man, there is no evidence to show that such absorption can either be responsible for skin or systemic cancer in man. Nevertheless, there is sufficient evidence that beryllium metal and several beryllium compounds are carcinogenic to at least three experimental animal species (rats, rabbits, and monkeys). This is another instance of a metal which is absorbed percutaneously but produces no skin cancer by any route.

NICKEL

Another metal which is absorbed through the skin and will also cause either irritation and, very frequently, allergic contact dermatitis, is nickel. Elemental nickel as deposited from inhalation of nickel carbonyl [$Ni(CO)_4$] and nickel salts, appears to be responsible for an increased incidence of lung and nasal cancer. This is most commonly observed in nickel ore reduction plants.

PLASTIC MONOMERS

1. Vinyl Halides

The widespread exposure to and use of monomers in the manufacture of plastics has led to investigations of their absorption and carcinogenicity. The first cases of angiosarcoma were observed in the early '70's among polyvinyl chloride workers forty years after the industrial process was initiated. About 90 cases have been observed throughout the world. The major route of absorption in these cases was probably by inhalation but skin absorption does occur. In addition to an increased risk for angiosarcoma there is also an excessive risk of death from brain and lung tumors and a possible increased risk of cancer of the digestive system. In none of the many studies conducted, however, is

there any mention of cutaneous carcinomas. Currently, because of cancer produced in experimental animals, vinyl bromide and vinylidene chloride are regarded as potential carcinogens in the workplace.

2. Styrene

The rate of percutaneous absorption of liquid styrene through the skin is 9-15 mg/cm^2/hr and, in an aqueous solution of 66-69 mg/l, is 40-180 mg/cm^2/hr. When applied to the human skin it can be found in subcutaneous fat for as long as three days after a recent exposure, and also may be found in expired air. The evidence of absorption may be measured in terms of the urinary metabolites mandelic acid and phenylglyoxylic acid. In an occupational exposure to styrene, an increase in the rate of chromosomal aberrations in cultured lymphocytes from peripheral blood was observed. Styrene has also been found to be mutagenic.

While polystyrene implants in animals will induce sarcomas, there is little information available on the cancer in humans attributable to styrene.

3. Acrylonitrile and Copolymers

Among persons exposed to acrylonitrile in certain textile fiber plants, there is an increase of lung cancer and colon cancer. The actual route of absorption, not well described, is assumed to be by inhalation. It has been

shown that when acrylonitrile is administered orally and by inhalation to rats, tumors of the forestomach, brain, and zymbal gland (a sebaceous structure) can be induced. It has also been shown to be embryotoxic, teratogenic, and mutagenic. In humans, skin exposure is a possible route of absorption but there is little information to demonstrate that percutaneous absorption will result in systemic or skin cancer.

4. Chloroprene

There is some epidemiologic evidence that chloroprene (2-chlorobutadiene) is associated with an increased incidence of both skin and lung cancer. Chloroprene is a monomer used in the manufacture of synthetic rubber (neoprene). It will also result in fetotoxicity and degenerative changes in the testes.

NITROSAMINES AND HYDRAZINES

Nitroso compounds are widely found in synthetic chemical reactions. When the nitroso group is attached to certain aliphatic amines such as in the case of nitrosodimethylamine, they become potent carcinogens. Nitroso compounds may be found in some insoluble cutting oils and also in soluble cutting fluids, and are suspect in their association with skin cancer from exposure to such cutting compounds. It has also been observed that NDELA or N-nitrosodiethanolamine

is an impurity found in many comestic products and is potentially toxic. It has also been observed that this nitrosamine is carcinogenic for rats by oral administration and in hamsters, if administered subcutaneously. The compound may result from a reaction of the di- or triethanolamine used in many cosmetic formulations with a nitrosating agent. It has been demonstrated by Bronaugh et. al., that NDELA is absorbed through intact stratum corneum. The permeability constant increased significantly in the presence of isopropyl myristate, a common cosmetic vehicle component.

Another nitrogen compound of significance because of its cutaneous effects and carcinogenicity is hydrazine. This compound and its derivatives: methylhydrazine, dimethylhydrazine and phenylhydrazine, are widely used compounds. Hydrazine, itself, is a cutaneous irritant. The hydrate is allergenic, the monhydrochloride used in a soldering flux had been found to be allergenic; thus demonstrating absorption of the material through human skin. Hydrazine was used as a torpedo propellant and later as a jet fuel and most recently it has been used as a rocket fuel in the United States. Both 1,1-dimethyhydrazine, and methylhydrazine have been used as fuels for rocket-propelled space vehicles. In addition to systemic toxicity, methylhydrazine and 1,1-dimethylhydrazine are regarded as having a risk for cancer on the basis of studies which have shown that rodents

exposed by inhalation developed lung tumors. Adenomas and some carcinomas were produced when hydrazine was administered in drinking water, by intubation, by i.p. injection and by inhalation. Hydrazine is a carcinogen in mice and rats, and the lungs are the primary target organ. Lung tumors are also produced by methylhydrazine as well as 1,1-dimethylhydrazine in mice. Based on this evidence, all types of exposure to hydrazine should be minimized, including contact with the skin or inhalation. The work areas as well as the persons exposed should be subject to strict regulation.

HAIR DYES

A number of substituted anilines and several azo dyes used in hair dye formulations have been shown to be carcinogenic in laboratory animals such as mice and rats by one or more routes of administration.

Skin absorption studies with hair dye components indicate clearly that they penetrate the skin and hence, systemic exposure to such compounds does occur and may result in cancer. Systemic cancers are known to be induced in laboratory animals by other carcinogens after skin application.

Certain azo dyes used in hair dye formulations contain the benzidine moiety and some of the compounds have been found to be metabolized "in vivo"

by animals and humans to the carcinogen, benzidine. Two of these dyes, Direct Brown 1:2 and Direct Brown 31, are still in use in some hair dye formulations.

Certain phenols used in hair dye formulations are known cocarcinogens from mouse skin experiments with benzo(a)pyrene as carcinogen. Similar experiments with aniline dyes as carcinogen have not been performed.

It should be pointed out that the epidemiologic data available to date are insufficient to incriminate hair dye components in human cancer.

Regulated Industrial Carcinogens

There are fewer than 20 agents which have been or still are used in industrial processes which are proven carcinogens, and their use is regulated (See Table 1). The skin is a major or secondary route of exposure for the following:

1. 4-Nitrobiphenyl

   The route of entry is by inhalation or skin absorption; it causes bladder cancer in humans. It is not used in industry currently.

2. α -Naphthylamine (1NA)

   It is absorbed by inhalation or by ingestion or through the skin. It is suspected of inducing bladder cancer in humans. It usually is contaminated with β-Naphthylamine. It is used in preparation of dyes and as an anti-oxidant for rubber, plastics and petroleum.

3. β-Naphthylamine (2NA)

   It is absorbed through the skin and by inhalation and ingestion. It was used extensively as a rubber anti-oxidant and dye intermediate but its use was discontinued. It is a potent carcinogen and produces bladder tumors in humans and cancer in rodents, dogs and monkeys.

4. 4,4-Methylene bis (2 chloroniline) (MOCA)

It is absorbed through the skin and by inhalation. It is used widely as a curing agent for epoxy resins and epoxy-urethane resins. It induces cancer in mice and rats.

5. Methyl chloromethyl ether (CMME)

It is absorbed by the skin and by inhalation. It is used as an ion exchange in manufacture of polymers, sugar, gelatin. It induces lung cancer in humans and lung and dermal cancers in mice.

6. 3,3-Dichlorobenzidine (DCB)

The major route is skin. It causes cancer of liver, bladder and breast in rats, mice, hamsters, dogs. There is no documentation for carcinogenesis in humans but it is usually associated with other carcinogens such as Benzidine.

7. Benzidine (2 aminodiphenyl)

The major route is skin. It induces bladder tumors in humans, primarily by absorption through the skin. It also is carcinogenic to rats and mice. It is an intermediate in the production of aniline dyes, rubber, plastics, printing inks, and is used in hospital laboratories.

8. 4-aminodiphenyl (4ADP)

It is absorbed by the skin and by inhalation, ingestion. It induces bladder cancer in man and dogs and tumors in rabbits and mice. It has not been used in industry since 1955.

9. Ethyleneimine (EI)

The route of absorption is percutaneous and by inhalation. It is used in production of rocket and jet fuels, and in flame-proofing, shrink-proofing, stiffening and waterproofing of textiles. It causes cancer in rats and mice and is extremely toxic to man.

10. ß-propiolactone

It is absorbed by inhalation and skin penetration. It is an intermediate in production of acrylic acid plastics and esters and used for sterilization of plasma, vaccines, tissue grafts, surgical instruments. It is readily absorbed through the skin and produces tumors in rodents.

11. 2-acetylaminofluorene (2AAF)

The route of absorption is by inhalation and the skin. It is not used in industry, only in laboratories. Its metabolites induce cancer in rodents, dogs, rabbits. The same metabolites are found

SUMMARY

I have attempted to review the mechanism of percutaneous absorption in relation to chemical carcinogens, and the factors which regulate and enhance transfer through the skin. I have reviewed some of the more significant aspects of the biotransformation systems in the skin which involve carcinogenesis. While historically, polycyclic aromatic hydrocarbons and arsenic are given the greatest prominence as chemical carcinogens for the skin, many other carcinogens have been identified as causing cancer of other organs after being absorbed through the skin.

There are at least three (3) metals: Cr, Ni and Be, whose compounds are absorbed through the skin. These are compounds which may induce lung cancer in humans through inhalation, but not skin cancer.

In the past 10 years much new evidence has been forthcoming to demonstrate association of certain plastic monomers with increased risk for systemic cancer through dermal absorption. Those cited are VCM, styrene, acrylonitrile and their copolymers. Nitro compounds for which skin is a potential portal and which increase risk for cancer are nitrosamines, hydrazines, certain substituted aniline and azo dyes. There are now about 13 industrial agents which are regulated in the United States.

The two types of studies that have increased our knowledge of and alertness to the increased risks for cancer in humans are:

1. Epidemiological studies: Cohort or Case Control Studies.

2. Animal exposures by different routes, including cutaneous.

TABLE 1

REGULATED CARCINOGENS

Asbestos

- 4-Nitrobiphenyl
- α-Naphthylamine
- β-Naphthylamine
- 4,4-Methylene bis (2-chloroaniline) (MOCA)
- Methyl chloromethyl ether (CMME)

  bis-Chloromethyl ether (BCME)
- 3,3-Dichlorobenzidine (DCB)
- Benzidine (2-aminodiphenyl)
- 4-Aminodiphenyl (ADP)
- Ethyleneimine (EI)
- β-Propiolactone
- 2-Acetylaminofluorene (2AAF)
- 4-Dimethylaminoazobenzene
- N-Nitrosodimethylamine
- Vinyl chloride
- Coke oven emissions