BETTER UNDERSTANDING THE CHEMICALS THAT SURROUND US

We live in a world where new chemicals — including those that contain smaller and smaller particles — are introduced at a rapid rate. What we don't know about these chemicals may hurt us. Read on to discover what we do know and how we can increase our knowledge about the chemicals we are exposed to in everyday life.

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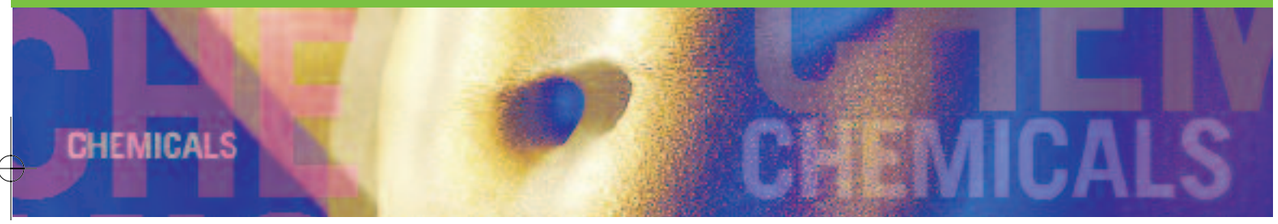

The skin is a complex and dynamic immunologic organ that also serves the primary function of maintaining a physical barrier to the environment. Yet, the skin is not a passive membrane. On the contrary, it is a viable tissue that can metabolize an assortment of environmental agents and act as a conduit. Skin absorption-penetration is a fundamental rate-limiting step in the amount of chemical internalized from the environment, and thus the skin plays a decisive role in shaping human environmental health and disease.

However, our skin is bombarded by an ever-increasing number of chemicals from products that we use, to foods that we eat, to the air that we breathe. Each year, more than 1,700 synthetic chemicals are introduced into the U.S. market, and many of these do not undergo basic testing.[1] In fact, of all the chemicals that are in use in this country — about 82,000 chemicals — only about 25% have undergone testing.[1] In addition, nanoparticles, particles smaller than 100 nm, are used with increasing frequency in new products. Not only are these particles more easily absorbed into the stratum corneum because of their small size, but to date no safe level of exposure to nanoparticles and nanomaterials has been established and products do not list how far into the epidermis and dermis these particles are absorbed.

As dermatologists, we are in a unique position to detect environmentally related disease, given the fact that the skin is a common site for toxicity manifestations. This article will discuss the growing number of environmentally caused diseases, the increasing number of chemicals we are exposed to, and the action that we as dermatologists can take to help identify skin-related diseases.

VULNERABILITY TO ENVIRONMENTAL ILLNESS

Vulnerability to illness is determined by a complex dynamic interaction between genetic and environmental risk factors. The World Health Organization Task Force for the Protection of Children's Environmental Health declared in its Bangkok statement that one-third of the global burden of disease can be attributed to environmental risk factors. And because they are potentially preventable causes of disease, environmental exposures deserve special attention.

In 1895. Josef Jadassohn, Professor of Dermatology and Syphilology at the University of Bern first described contact allergy to mercury, giving birth to the inceptions of patch testing.[2] "Prior to this time, and indeed for some years thereafter, contact hypersensitivity was essentially unknown except by few…in dermatology."[3] By the 1920s, landmark articles were debuting around the globe from Sulzberger in America to Low in England. Low published an account on skin-sensitiveness to non-bacterial proteins and toxins in the British Journal of Dermatology[4] and introduced the concept that chemicals in our environment (acids, alkalis, iodoform, formalin, hair-dye and chemicals inside plants) are capable of producing injury to the skin ("irritation and dermatitis").[4] And, in his first edition, Fisher wrote that his book "may be read as a 'detective' story which can have a happy ending only if the culprit is identified, eliminated, and injuries mended."[5]

TRENDS ON TOXICOLOGY

Each year new chemicals that are committed to making our lives easier and adding to our creature comforts come to market. For example, non-wrinkle shirts, stain-resistant pants, unbreakable bright colored toys, disposable tableware, microwaveable plastics, potent cleaning supplies and fire-resistant mattresses stock the shelves of supermarkets and convenience stores. Furthermore, there is 'Stay Fresher Longer Tupperware', antibacterial clothing and tennis balls with more bounce (all nano-technology based products).

This "easier and more care-free approach" to our daily routine, however, may translate into an increase in exposures to uninvestigated, suspected or confirmed chemicals with potentially serious injurious health effects. The warning signs abound, suggesting the price we might be paying for this approach, as the prevalence of environmentally related chronic diseases has dramatically risen in the last 30 years. (**See Table 1**.)

Theophrastus Phillipus Auroleus Bombastus von Hohenheim (1493-1541) also referred to as "Paracelsus", formulated what is known as "the central dogma of toxicology" –"All things are poison and nothing is without poison; only the dose makes a thing a poison," a quote that is often condensed to "The dose makes the poison."

Disregarding the classic assumptions of traditional toxicology, some new chemicals exert serious adverse effects at levels of exposure well below the hazardous doses observed in animal studies. For example, phthalates, pesticides and alkylphenols, have been found to be endocrine disruptors at very low doses. On the other hand, well known chemicals such as lead which once were thought to have a "safe" level of exposure are now associated with brain damage when children are exposed to those levels.

Furthermore, the hazard deemed by a chemical, will not only be related to its dose. Route of exposure (ingestion, inhalation, dermal) and time point of exposure (*in utero*, childhood), volatility or reactivity of the chemical will also play an important part. Of course, the wide range in individual responses due to genetic variability cannot be forgotten. In addition, repeated and combinatorial exposures to multiples of chemicals at one time, may also have compounded deleterious effects since chemicals may have additive or even synergistic effects. The synergistic effect of tobacco smoking and asbestos exposure, for example, increase the risk of lung cancer by 25-fold,[6] further illustrating this point.

The average American is exposed simultaneously and sequentially to multiple environmental chemicals from various sources on a daily basis,[7] most of which have never been tested for health hazards. (**See Table 2**.)

In fact, of the 1,700 new synthetic chemicals being brought to the U.S. market annually, the Environmental Protection Agency (EPA), founded in 1970 to protect human health and safeguard the natural environment), tests only chemicals that demonstrate evidence of significant health risk potential.[8] This translates into the reality that only 25% (of the 82,000 chemicals in use in the U.S.) have ever been subject to a basic testing.[1]

ASSESSING THE HAZARDS

Unfortunately, risk alerts on environmental hazards often come only after significant evidence emerges or an epidemic of inadvertent acute intoxication takes place.

A good example is the disaster that occurred in Minamata Bay, Japan, in the early 1950s, where local villagers ate fish contaminated with industrial residues of methyl mercury and began to exhibit signs of severe neurological damage (i.e., visual and hearing loss, extremity numbness, psychiatric disturbances, ataxia, and neuropathy).[9]

Cutaneous changes included contact dermatitis, burning of the face, grey or blue–black facial discoloration, flushing, erythroderma, purpura and gingivostomatitis.[10] Babies exposed to methyl mercury *in utero* were the most severely affected members of the village. Since methyl mercury is lipophilic and readily crosses the blood-brain and placental-fetal barriers, these infants demonstrated diffuse and widespread neuronal atrophy.

Mercury was also discovered in the breast milk of the mothers and evidence unfolded that these babies' exposures continued after birth, which led to chronic sequelae including seizure disorders, profound developmental delay in motor and language function and renal damage.[11]

Fish from contaminated waters are the most common culprits for methyl mercury, the most toxic form of this metal. Industrial inorganic mercury is converted by aquatic organisms and vegetation in waterways to methyl mercury. Larger species of fish such as swordfish, shark, and large tuna, eat contaminated vegetation, and the mercury becomes biomagnified.[12] Fish proteins bind more than 90% of the consumed methyl mercury so tightly that even the most vigorous cooking methods

THE MANY SUSPECTS OF ONE ENVIRONMENTAL-BASED ILLNESS

Contact dermatitis can be caused by myriad suspects. Alexander A. Fisher illustrated this point when he said,

"I have indicated that in the search for causative agents of contact dermatitis the physician must literally suspect everything 'under the sun' (and the sun, itself), including those agents to which the patient has been exposed for years without prior difficulty. The patient's total environment with its flora and fauna, topical medications, clothing, cosmetics and other contactants encountered in work or play may have to be investigated. The victim must then be armed with knowledge that will enable him to distinguish friend from foe and to avoid his personal villains no matter how disguised. Thus, the victim, the patient, will be enabled to enjoy his environment with safety."

Table 1. ENVIRONMENTALLY RELATED HEALTH DISORDERS

- **Contact Dermatitis** affects 72 million people in the United States and is the third most-common reason for patients to seek consultation with a dermatologist, accounting for 9.2 million visits in 2004 alone.[i] Additionally, there were 5 million visits to primary care physicians for eczema and an unexplained dermatitis.[ii] An increasing prevalence of contact dermatitis led the National Institute for Occupational Safety and Health to form a research component that deals specifically with allergic and irritant contact dermatitis.[iii]

- **Eczema** is one of the most common skin diseases in infants and children, and has increased at least 30% since 1970, according to the American Academy of Dermatology. Some researchers have found a dose-response relationship between the concentrations of phthalates (a widely used plasticizer) in the dust and the likelihood of being diagnosed with eczema. The higher the concentration, they say, the more likely a child is to be diagnosed with eczema.[iv]

- **Asthma** has roughly doubled in frequency since 1980[v] (#1 cause of pediatric hospitalization, #1 chronic health condition among children and leading cause of school absenteeism attributed to chronic conditions[vi]). Chemicals such as methacrylates, colophony, epoxy resins, paraphenylenediamine, metal fumes (chromium, cobalt, nickel etc.) plastic fumes (PVC, polyethylene, polypropylene), formaldehyde and some pesticides can cause or contribute to asthma mainly in the workplace.[vii]

- **Brain cancer** is increasing in children. From 1973 to 1994, the number of reported brain tumors in children under 15 increased 1.8% per year.[viii] Ionizing radiation is the only established environmental cause of brain tumors.[ix] Other environmental agents that have been suggested to contribute to this type of cancer are pesticides. A common pesticide used in the past by dermatologists to treat head lice and scabies, lindane, is linked to a five-fold increased risk of brain tumors.[x]

- Learning disabilities, attention deficit hyperactivity disorder (ADHD), developmental delays, and emotional and behavioral problems are among childhood disabilities of increasing concern. For example, the number of children entered into the California **autism** registry increased by 210% between 1987 and 1998.[xi] Improved reporting and differing diagnostic definitions undoubtedly explain some of the increase of this disorder, but they do not explain the entire pattern.[xii] Extensive laboratory and clinical studies of several toxicants including lead, mercury, PCBs, pesticides, PBDEs and solvents such as toluene, have demonstrated the unique vulnerability of the developing brain to these types of environmental agents.[xiii]

- Over the last 25 years, the incidence and severity of **hypospadias** (a birth defect characterized by an abnormality of the penis in which the urinary tract opening is not at the tip), has reportedly doubled in the United States and Europe.[xiv] Recent studies implicate exposure during pregnancy to environmental endocrine disruptors such as dioxins with an increase in hypospadias.[xv]

i Most prevalent skin diseases impact millions of Americans burden of skin disease study finds several diseases to be quite common. *Dermatology World*. 1:24, May 2005.
ii R.S. Stern, Dermatologists and office-based care of dermatologic disease in the 21st century. *J Investig Dermatol*. Symp 9 (2004):126–130.
iii NIOSH (The National Institute for Occupational Safety and Health), Allergic and irritant dermatitis. Additional information (2006).
iv Broenehag CG, et al. The association between asthma and allergic symptoms in children and phthalates in house dust: A nested case control study. *Environ Health Perspect*. 2004;112:1393-1397
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xii Byrd RS. The epidemiology of autism in California: A comprehensive pilot study. Report to the legislature on the principle findings.
xiii Schettler T. Toxic Threats to neurologic development of children. *Environ Health Perspect*. 2001 Dec;(109 Suppl 6):813-816.
xiv Paulozzi LJ. International trends in rates of hypospadias and cryptorchidism. *Environ Health Perspect*. 1999 Apr;107(4):297-302.
xv Toppari J. Environmental endocrine disrupters and disorders of sexual differentiation. *Semin Reprod Med*. 2002;20(3):305-312.

like deep-frying, boiling, baking, or pan-frying cannot remove it.[13]

The U.S. Environmental Protection Agency has recently developed a reference dose for mercury of 0.1 mg/kg/day.[14] Unfortunately according to the EPA, 52,000 to 166,000 pregnant women in the United States consume fish contaminated with mercury at levels at or above this reference dose.[15]

"Minamata Bay" was not the only large-scale human mercury poisoning incident. For example, in the early 1970s, one of the most severe mass poisonings in history occurred in Iraq when nearly 95,000 tons of seed grains treated with a methyl mercury–based fungicide were accidentally baked into bread for human consumption.

More than 6,000 individuals were hospitalized, and 459 died. Many persons were hospitalized over several weeks before methyl mercury intoxication was correctly diagnosed.[16]

When it comes to global allergen prevalence and skin sensitivity, however, epidemic accidental acute intoxications are not the norm. Instead, we rely on the accumulation of significant evidence and the observations of astute persons who recognize the association of chemicals in a given person's environment with their clinical picture.

Furthermore, "New sensitizing chemicals and products are continuously being introduced. Hence, the selection of substances for a standard test cannot be rigidly defined. Constant revision and additions are needed to adapt the standard series to the sensitivities currently prevalent in the population served by the clinic."[17] Detecting and identifying hazardous chemicals in our environment is difficult when these agents have been newly introduced into it.[18]

HAZARDOUS ENVIRONMENTAL CHEMICALS IN CONSUMER PRODUCTS

The National Center for Environmental Health (NCEH) defines an environmental chemical as any chemical compound or chemical element present in air, water, food, soil, dust, or other environmental media. Consumer products, such as personal hygiene products and consumables are a growing component of our overall environmental media.

When one of the several millions of environmental agents exhibits a potential or confirmed adverse health effect, terminology changes and this chemical is then referred as a "toxic environmental chemical"[19] or simply as a "hazardous environmental chemical."

Because consumer products constitute a very important aspect of our environment, they are significant contributors to our level of exposure to chemicals. Unfortunately, an increasing number have been shown to be key sources of hazardous environmental chemicals.

Exposure to these products may be directly associated with environmental-induced medical conditions such as irritant and allergic contact dermatitis, the most common skin diseases of environmental origin.[20]

THE GROWING TREND OF NANOTECHNOLOGY

New technologies are constantly applied to novel consumer products created with innovative fabrication techniques. For example, in the last two decades, we have seen a revolution in the types of personal hygiene products available, with the introduction of nanotechnology into their manufacturing. "Skin care is definitely becoming a big area for nanoscience" said Neil Gordon, president of the Canadian Nanobusiness Alliance.

While, Eric Drexler (1972) and Richard Feynman (1950s) were among the first to use the term "nanotechnology," it was Norio Taniguchi in 1974 who used the term to specifically describe the manipulation of compounds smaller than 100 nm called nanoparticles (NP).

Their tiny sizes have enabled scientists to manufacture new products capable of performing unique and specialized tasks. For example, zinc oxide particles were incorporated into sunscreens, which changed the classic opaque and greasy texture into a clear vanishing elegant feel.

Likewise, emulsions fragmented into nanometer size were found to be less oily, while allowing for deeper penetration and increased concentrations of active ingredients delivered to skin and hair.[21] This led these engineered nanomaterials (NM) to also be used in creams, cosmetics, in foods as nutraceuticals, and in pharmaceuticals.[22]

Given the growing utilization of the NM, it is alarming that to date manufacturers have yet to publish the degree or depth of penetration of NP in their products.[22] This is despite the fact that some products have been formulated with "penetration enhancers" ostensibly to deliver active ingredients to the deep epidermis and superficial dermis.

Results from initial skin absorption studies have been variable and mixed when establishing the ability of NP to penetrate the skin. Some studies reported in the literature that particles as small as 1000 nm can enter undiseased skin while particles 7000 nm in size or smaller penetrate skin that is damaged.[23]

On the other hand, Robert Bronaugh from the Office of Cosmetics and Colors at the FDA, stated during the Third International Conference on Occupational and Environmental Exposure of Skin to Chemicals 2007 (recently held in Golden, CO) that, "Initial studies suggest little-to-no normal skin penetration of NP from topical formulations beyond the stratum corneum; however, there is still the challenge of studying the penetration of NP in skin with altered barrier function."[24]

In this aspect, simple acts such as shaving, or injuries such as sunburns, cuts or scrapes can increase cutaneous permeability. Occluded skin (in the genital or axillary folds, for example for hygiene products) or thin skin (such as the eyelids, for make up) may be particularly vulnerable.

Once they enter the skin, NP can be allergenic or harmful at a variety of cellular and subcellular levels[25] potentially inducing injurious responses. For example, nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NFD/NSF), is a recently described *de novo* disease that affects the skin and viscera in some patients with renal failure. It has been strongly associated with exposure to gadolinium-based contrast agents. Gadolinium deposition has been identified and quantified in the affected skin of patients with NSF[26,27] In other cases, the gadolinium has appeared entrapped within intracellular lysosomes.[26] (**See Figure 1, on page 44**.)

Table 2. ENVIRONMENTAL CHEMICALS ENCOUNTERED IN AMERICAN DAILY LIFE*

*Chosen on the basis of data by the NCEH that suggests exposure to these chemicals in the American daily life plus the seriousness of the health effects known or suspected to result from exposure to them.

PHTHALATES

Approximately 3.5 million metric tons of phthalates are produced each year worldwide for use in soft polyvinyl chloride (PVC) products such as shower curtains, rainwear, toys, and cable sheathing. When not added to PVC, phthalates are used in fragrances, hairsprays, nail lacquers, lotions, paints, adhesives and pharmaceuticals. A product test conduced by the Environmental Working Group showed phthalates in nearly three-quarters of 72 name-brand personal care products tested, but none of this contained the word "phthalate" in their ingredient label; instead, phthalates were hidden in the product's fragrance.[1] Seventy-five percent of the environmental release of phthalates occurs during the use of products containing them. Phthalates pass through placenta and breast milk. Exposure in humans has been associated with allergic contact dermatitis[2] and premature breast development in females.[3] Animal studies suggest phthalates affect male reproductive development and semen quality via inhibition of androgen biosynthesis.[4]

PESTICIDES

In America, 90% of households use pesticides.[5] Exposure can also be at school, at work and through eating food with pesticide residues. Population-based studies in the U.S. show that over 90% of children have detectable urinary residues of just one of at least one of the neurotoxic organophosphate pesticides, and >50% of the population contained at least six.[6] Another study examined the meconium of newborns and found residues of organophosphate pesticides in each of them, documenting fetal exposure during critical periods of brain development.[7] There is striking evidence that inadvertent exposure to these chemicals can cause a whole variety of acute and chronic health hazards. Yet, their labels show only the acute effects. Pesticides are a well known cause of both irritant and allergic contact dermatitis mainly in exposed skin areas of farm workers,[8] and can be diagnosed by comprehensive patch testing. Organophosphates and carbamates are neurotoxins that may lead to altered neurological functioning and neurodevelopment in humans.[9] DDT is also considered an hormone disruptor and has been correlated with pre-term birth. Permethrin is considered by EPA a possible human carcinogen and may affect human immune and reproductive systems. Malathion may cause reproductive damage, genetic mutations and immune system alterations.[10]

POLYBROMINATED DIPHENYL ETHERS (PBDEs)

PBDEs are one three groups of flame retardants used in furniture, televisions, carpeting, mattresses and hair dryers. High levels of PBDEs have been found planetwide in air, water, fish, birds, and marine mammals. Ingestion is regarded as the most likely route for PBDE exposure through contaminated food, but air inside homes can carry high concentrations of these flame retardants. Studies in rodents suggest that deca-BDE (the one used in plastics, textiles and electrical components) may be a possible human carcinogen, while octa-BDE and penta-BDE have possible endocrine (especially thyroid), hepatic, reproductive, and neurodevelopmental toxicities.[11] In 1998, Bergman et al reported for the first time the presence of PBDEs in human breast milk. Of note, skin hasn't been studied as a possible route of absorption of PBDEs.

COTININE

Cotinine is a metabolite of nicotine, and levels of cotinine in blood track exposure to environmental tobacco smoke (ETS) in people who do not smoke. Higher cotinine levels indicate more exposure to ETS which has been identified as a human carcinogen. Children's levels are more than twice those of adults.[11]

CADMIUM

Recent research studies have shown that urine cadmium levels as low as 1 mg per gram of creatinine in people may be associated with subtle kidney injury and with an increased risk for low bone mineral density. About 5% of the U.S. population aged 20 years and older has urinary cadmium levels at or near these levels. Cigarette smoking is the most likely source for these higher cadmium levels.[11] Of note, the yellow color in tattoos has been ascribed to cadmium sulphide.[12]

Table 2. ENVIRONMENTAL CHEMICALS ENCOUNTERED IN AMERICAN DAILY LIFE *(CONT'D.)*

FORMALDEHYDE

The eleventh most common contact allergen according to 2000-2001 NACDS data is a commonly used preservative for cosmetics and personal care products such as shampoos, soaps and baby formulations, dishwashing detergents, room deodorants, tobacco cigarettes and permanent press clothing. It is also used as a base for plastics, as a glue, in bonded leather, and in construction materials. It represents 5% of the U.S.'s gross national product.[13] Notable detrimental health effects of inhaled formaldehyde include sensory irritation, triggering of acute asthma attacks and potential cancer of the upper respiratory tract.[14]

ALKYLPHENOLS (APs)

APs are used as additives in cosmetics, textiles and food packing, as well as emulsifiers in latex paints and pesticides. They are present in fiberglass, polystyrene products and polycarbonate plastics. The alkylphenols, especially bisphenol A are potent endocrine disruptors[15] that have the ability to mimic natural estrogen. Bisphenol A (DGEBA) is the monomer and most important contact allergen in epoxy resin and it can be patch tested at a concentration of 1% in petrolatum. Epoxy resins of the Bisphenol F type (DGEBF) can also be patch tested at the same concentration. Bisphenol A can migrate from the plastic of baby bottles and other water containers into the liquid or food, thereby causing a health concern. Furthermore, when these bottles are subjected to dishwashing, boiling and brushing, the polymer degrades and a significant increased release of bisphenol A can occur.

POLYCHLORINATED BIPHENYLS (PCBs)

PCBs are a family of dioxin-like chemicals that were used as insulating fluids and lubricants in the manufacture of electrical equipment and paints.[16] For a period of 30 years, PCBs were discharged into the upper Hudson River, and as a consequence of this contamination from above Albany to lower Manhattan, this river has been declared by EPA to be the nation's longest superfund site. Finally, in 1976 their production was halted because of their extreme environmental persistence and the concerns that they could cause cancer. Consumption of contaminated fish and shellfish is the most important route of human exposure.[17] PCBs are fat-soluble and they accumulate in the marine food chain, reaching very high concentrations in predator fish such as striped bass and bluefish, and in predatory bottom-feeding species, such as crabs, eels and lobsters. PCBs can cross the placenta.[18] Children whose mothers had eaten contaminated Lake Michigan fish during pregnancy were found to have deficits in fetal and postnatal growth and poor short-term memory in infancy.[19] Similar observations were made in Japan when more than 1,000 people became ill after ingesting rice oil contaminated with PCBs. After this massive poisoning known as the Yusho Incident, children exposed prenatally to PCBs demonstrated low birth weight, abnormal skin hyperpigmentation, slow development, delayed developmental milestones, clumsy movements and lower IQs.[20]

Finally, but very important to the dermatologic field, is the fact that exposure to PCBs can cause chloracne, a unique skin condition involving the skin follicles. This clinical presentation is a hallmark of PCB exposure in humans.[21]

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While aqueous ionic chemistry may be involved in early transmetallation reactions, nanoparticle-sized conglomerations of this toxic metal could alter cytokine production within fibrocytes or other infiltrating cells, such as circulating fibroblasts. (Personal communication with Whit High, M.D., May 2007.) In this regard, NSF could be the first example of a disease with cutaneous manifestations with at least a partial basis in nanoparticle theory (according to co-author Adnan Nasir, M.D.).

THE SLUDGE FACTOR

Nanoparticles, which are otherwise inert, have the potential to aggregate with one another[28] and "sludge". Sludging of NP could also have the potential to theoretically affect ducts and pores in the skin (possibly leading to conditions such as chloracne, perioral dermatitis, acne, rosacea or sebaceous hyperplasia), in the eyes (theoretically causing styes, blepharitis, chalazions) or those of the reproductive system theoretically leading to infertility in males and females (according to co-author Adnan Nasir, M.D.).

Of interest, the cosmetic industry is investing in this new technology to meet the growing demand for newer consumer products.[29] In fact, the sixth-largest patent holder of nanotechnology in the United States is a cosmetic company (L'Oreal). As youth and beauty are the primary goals of this industry, young women of childbearing potential may be the targets of cosmetic marketing. The health consequences of accumulated nanomaterials used (over several decades or during pregnancy, on fetuses) is not known. And, yet the over-the-counter skincare market is currently estimated at $12 billion per year and annual sales of facial products account for $7 billion in the United States. By 2012, it is expected to be a $2 trillion industry employing over 2 million workers in the United States.[30]

BIO-MONITORING OF CHEMICALS

Investigation for sources of contact dermatitis in personal care products can be evaluated through closed epicutaneous patch testing by the physician or repeat open application testing (ROAT), in which the individual tests the product in question repeatedly on themselves. Both these investigative measures can be a safe and effective; however, continued ROAT testing and updating of "screening allergens" is necessary given that the composition of such products is ever-changing.[31]

Importantly, Epstein et al emphasized that "patch test screening only supplements, but never supplants, patch testing with suspected environmental agents. No screening series could ever encompass the many allergens encountered in cosmetics, industry and gardening for example."[3]

In the United States, several agencies and institutions work to establish the levels for health concern for individual substances. For example, the Environmental Health Laboratory of the NCEH assesses people's exposure to these environmental chemicals through bio-monitoring the chemicals or their metabolites in blood and urine samples from a random selection of participants. These are selected from the National Health and Nutrition Examination Survey that is conducted by Center for Disease Control's (CDC) National Center for Health Statistics. According to the CDC and the NCEH, bio-monitoring measurements are the most health-relevant assessments of exposure because they measure the accumulating levels of the chemical in people from all environmental sources (e.g., air, soil, water, dust, food or consumables); they combine and provide information to study environmental exposure rates.

The current (2005) Third National Report on Human Exposure to Environmental Chemicals provides information on the exposure of the American population to 148 chemicals over the period from 2001 to 2002.[32] (**See Table 2 for a selection of these chemicals**.) While the report attempts to establish reference ranges for these chemicals, it does not establish a correlation between a specific exposure dose and a specific health hazard.

Likewise, "safe" levels of exposure to nanoparticles and nanomaterials have not been established. Some near-nanoparticles, such as zinc oxide and titanium dioxide, have already received FDA indication for their use in sunscreen.

PROVIDING NEW CHALLENGES

These new chemical compounds may confront medical science with new challenges. In dermatology for example, the introduction of products containing nanoparticles that come in contact with the skin might represent a whole new class of irritants, allergens, haptens, cross-reactants, and unanticipated particle-particle interactions that may lead to disease.

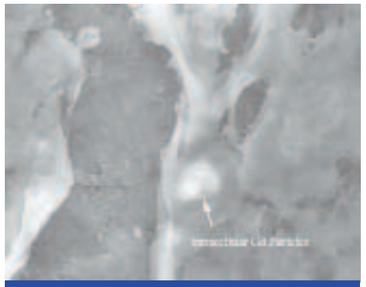

Figure 1: Intracellular particles of gadolinium, a chemical that is used as an MRI contrast agent and has also been detected in the skin of patients with nephrogenic fibrosing dermopathy/ nephrogenic systemic fibrosis.
Image courtesy of Whit High, M.D.

In assessing the health hazards of these compounds, host and environmental factors evaluation will be important.[19] With "global warming", dispersal of hazardous material (Hazmats) is expected to be greater and with dwindling freshwater supplies, the concentrations of Hazmats in the water supply is expected to increase.

Unfavorable host factors might include concomitant skin diseases, such as atopic dermatitis, contact dermatitis, acne, seborrheic dermatitis, and psoriasis, which could make the skin more permeable to allergens and nanomaterials.

Seeking the fountain of youth may be another unfavorable host factor, particularly for women of childbearing potential. Furthermore, skin permeability and percutaneous absorption become a rate determining step for human health risk assessment, when dermal exposure to certain environmental chemicals is involved.

By following a multistep allergic contact sensitization risk assessment process, new chemical substances can be identified as contact allergens. The risk assessment process is a comparative approach in which data on the inherent hazards of a material and the exposure to it (through manufacturing or con-

Table 3. ENVIRONMENTAL CHEMICALS ASSOCIATED WITH SKIN DISEASE

DISEASE	STRENGTH OF EVIDENCE FOR ASSOCIATION		
	STRONG	GOOD	LIMITED
Alopecia[1]		arsenic, boron, gold, thallium	selenium
Chloracne	PCBs and dioxins,[2] organo-chlorine pesticides (DDT)[3]	pentachlorophenol (PCP)[4]	nanoparticles (NP)[3] (theoretically)
ACD[1,2]	aromatic amines, dyes, colophony, epoxy resins, formaldehyde, fragrances, glues and bonding agents, latex, metals, herbacides, pesticides, potassium dichromate, preservatives, rubber products etc.		
ICD[1,2]	abrasive dust, cement, coal tars, detergents, soaps, ethylene oxide, acids, alkalis, metals, pesticides, solvents etc.		
Erythema Multiforme			organophosphates (pesticides)[3]
Hyperpigmentation			PCBs
Leukoderma	alkylphenols	ethylene oxide	carbamates (pesticides)[3]
Photosensitivity		para-aminobenzoic acid derivatives, hexavalent chromium compounds, coal tars, pesticides[3]	
Dermatomyositis			silica[4]
Scleroderma	silica*[5]	solvents (including: aromatic mixes, benzene, carbon tetrachloride, paint thinners/removers, trichloroethane, trichloroethylene [TCE], toluene and xylene); vinyl chloride	epoxy resins, herbacides, mercury, silicone, metaphenylenediamine, tetrachloroethylene
Vinyl Chloride Disease, Acro-osteolysis**	vinyl chloride		
Melanoma[6]			asbestos, formaldehyde, carbon tetrachloride, pesticides[7]***
Skin Cancer (Non-Melanoma)[2,6]	coal tar+, mineral oils+, shale oils+ arsenic+ *****	aromatic amines, ethylene oxide, anthracene, benzopyrene#, pesticides[7] (arsenicals)	acrylamide^, vinyl chloride
Acne[2]	asphalt, crude, cutting and lubricating oils, greases, petroleum		nanoparticles (NP) (theoretically)
Rosacea			nanoparticles (NP) (theoretically)

* Occupational silica exposure has been associated with the development of scleroderma in males but not in females.
** Affected workers polymerizing vinyl chloride in 1960s. Patients developed finger paresthesias, cold sensitivity, Raynaud's phenomenon, pseudo-clubbing of the fingers, skin edema and thickening of the fingers, hands and forearms.
*** Asbestos, carbon tetrachloride, formaldehyde and pesticides have been associated with intra-ocular melanomas.
***** Skin cancer caused by arsenic can take over 30 years to manifest.
\+ Group 1 human carcinogen = carcinogenic to humans - according to the International Agency for Research on Cancer (IARC).
\# Group 2A human carcinogen (IARC) = probably carcinogenic to humans.
^ Group 2B human carcinogen (IARC) = possibly carcinogenic to humans.

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sumer use or foreseeable misuse) are integrated and compared with data generated on benchmark materials of similar or product application or both. The steps included are:

1. analytical characterization and literature review for skin sensitization data
2. preclinical skin sensitization testing (murine local lymph node assay/or Buehler guinea pig test)
3. human repeat insult patch testing
4. clinical use testing
5. monitoring and follow-up of consumers' comments.[33]

However, this process is not universally practiced because cosmetic products are not subject to pre-market approval by the Food and Drug Administration (21 U.S.C. §361). The manufacturer of a cosmetic product is the one responsible for the safety of the product and its ingredients and the FDA regulates only when "claims" are made by the product developer. If there is no claim made by the manufacturer regarding product performance or capability, FDA regulatory jurisdiction is not applicable.[34]

DERMATOLOGISTS ON THE FRONTLINES

Dermatologists serve on the frontline because we routinely encounter patients with environmentally related disease, given the skin's important role as a barrier to hazardous chemicals, as well as a common site for toxicity manifestations.

Environmental dermatology is definitely a growing field because skin diseases comprise a significant segment of environmentally related diseases[35] (**see Table 3**), and the skin is in most cases the target of the ever-increasing number of personal care products that might contain potentially hazardous chemicals.

It is important to understand the implication of the skin and its functions (permeability, absorption, and metabolism) in the development of environmentally related diseases. At this point, more than 3,700 chemical agents have been implicated as causal agents in allergic contact dermatitis and more than 65,000 chemical agents have been identified as causal agents in irritant contact dermatitis in humans.[35]

The 2004 Burden of Skin Disease study determined that 72.9 million persons that year were suffering from contact dermatitis. In stark contrast, an estimated 140 comprehensive patch testers exist in the United States (identified through the American Contact Dermatitis Society membership).[36]

With the accelerating number and types (nanoparticles and other nanomaterials) of chemicals being introduced into the environment, dermatologists are in the unique position to participate in the evaluation, screening, testing, and monitoring of these new product technologies and to advise practitioners and patients. Furthermore, a growing opportunity exists to work hand in hand with industry to identify avenues for future potential developments, pitfalls, and design alternatives, early in the manufacturing process. This collaborative process could eliminate costly investments on products with predicted or potential injurious effects.

Ultimately, through increased awareness of possible harmful agents (both active and inert) in our environment, which includes personal hygiene products, medicaments and personal effects, we can work toward safer products and "be enabled to enjoy …[our]…environment with safety."[5]

The delicate balance between using technology to support our ever-growing population and its potentially hazardous consequences must be continuously adjusted for optimal overall outcome. ■

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