

Recent Approaches to Toxicity Prevention in Animals

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Abstract: Acute or chronic exposure of animals to concentrations of toxic chemicals beyond the minimum permissible exposure level induces deleterious health effects including terminal malignancies. Regulatory agencies have assigned acceptable levels of exposure, known as permissible exposure levels (PELs), time weighted averages for 8 hours of exposure (TWAs) and no observed effect concentration values (NOECs) at which exposures presumably have no toxic effects. Many pollutants, such as heavy metals and persistent organics, bio-accumulate in the body, and remediation strategies to remove these chemicals from the environment are extremely difficult and capital intensive. Environmental pollutants induce signaling pathways that respond to oxidative stress; these same pathways are associated with the etiology and early pathology of many chronic diseases. Consequently, strategies that modulate the effect of toxicants on pathophysiologic processes involved in disease etiology and progression will be of public health importance. Clients, clinicians, nutritionists, policy makers and regulatory agencies have a major role to play in surveillance, monitoring and prevention of toxicity especially in high risk population.

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Introduction

Toxicity refers to the degree to which a substance (toxin or poison) can harm animals (Gupta, 2000). Prevention of toxicity refers to the various processes and strategies that can be put in place to avert toxic or poisonous substances from causing harm to individuals. Common sources of toxicity include industrial wastes, feed, water, plants, poisonous animals, metals, chemicals, drugs and radiation exposure. Toxicity could either be acute, sub-acute, or chronic depending on the duration of exposure to the toxic substance. Acute exposures to high concentrations of toxic chemicals have been known for a long time to induce predictable deleterious health effects, but low concentrations of such chemicals have historically been believed to be benign to humans. In fact, regulatory agencies have assigned acceptable levels of exposure, known as permissible exposure levels (PELs) time weighted averages for 8 hours of exposure (TWAs) and no observed effect concentration values (NOECs) at which exposures presumably have no toxic effects (Zeliger, 2011).

There is no “easy fix” to protect or intervene against diseases associated with exposure to environmental pollutants. Many pollutants, such as heavy metals and persistent organics, bio-accumulate in our bodies, and remediation strategies to remove these chemicals from the environment are extremely difficult

and costly. Furthermore, many environmental pollutants induce signaling pathways that respond to oxidative stress; these same pathways are associated with the etiology and early pathology of many chronic diseases (Hennig *et al.* 2005). Therefore, strategies that modulate the effect of toxicants on pathophysiologic processes involved in disease etiology and progression will be of public health importance.

General Toxicity Prevention Strategies In Small Animals

Prevention of toxicity in household pets consists of controlling the animals’ environment to decrease exposure to potentially dangerous substances. This requires animal caretakers to be diligent and knowledgeable of potential risks. Clients should be reminded to keep all veterinary and human medications, both prescription and over-the-counter (OTC), out of the reach of animals. Since some pets are able to climb onto high surfaces and open cabinets, medications are not adequately “out of reach” in those places. Owners should be instructed not to give their pets any medication, including their own, unless directed by their veterinarian. Clients may not realize that giving an OTC medication that they consider safe, like acetaminophen, could cause life threatening illness in their pet. For example, treatment of alopecia in cats with topical minoxidil solution has led to pleural effusion, pulmonary edema and death (DeClementi *et al.*, 2004). Clients should also store all other potentially hazardous

products, including cleaning products, auto-care products, pesticides and insecticides, out of the reach of their animals. Garbage cans should be sealed with tamper-proof lids (DeClementi *et al.*, 2004).

Animal caretakers should be urged to read all label information before using a product on an animal or in the animal's environment and to follow the label instructions exactly. Veterinarians should mention that it is often not safe to use a product on an animal species for which it is not intended. For example, using a concentrated permethrin flea product labeled for dogs could prove deadly if used on a cat (Richardson, 2000a).

Since many plants are poisonous, clients will want to be aware of the plants in an animal's environment, including those in outside areas. Additionally, they should be alert to any fluids leaking from vehicles and clean up leaks immediately (Richardson, 2000a).

If a rodenticide or other bait is necessary in the home or yard, the product should be placed in an area that is completely inaccessible to non-target animals. The bait should be removed as soon as it is no longer needed. An animal's enclosure should be routinely checked, and unfamiliar or questionable items removed. Companion animals should be supervised, when possible, if they are outdoors, and a securely gated, confined area should be provided when animals are left unattended (Richardson, 2000a).

The guidelines for keeping household pets safe from poisoning are very similar to those for children, especially toddlers. Some pets may even be more at risk than children because, unlike children, they are commonly left unattended. They are also likely to chew open some containers, including those considered child-safe.

In Large Animals

Decreasing the risk of exposure to toxicants is also important in large animals. Caretakers should be urged to purchase hay and feed from reputable suppliers, to examine the feed for recognizable contamination, and to verify cleanliness and high quality (Osweiler, 2001). Feed should be stored in a clean, insect-free area at the appropriate moisture level to prevent damage and lessen the risk of contamination or mycotoxin growth (Osweiler, 2001). Learning to identify poisonous plants and their potential effects is critical for large animal clients. Once poisonous plants have been recognized in an area, many strategies can be employed to limit exposure. The most effective strategy is to remove animals from poisonous plant-infested areas either by herding or fencing off those areas (Cheeke, 1998). If this is impossible, attempts should be made to reduce the poisonous plant populations via mechanical (burning or pulling), chemical (herbicides), biological (such as using the larvae of the cinnabar moth to control tansy ragwort), or other control methods. Since treatment with herbicides may increase palatability or

toxicity in some plants, animals should not be allowed access to herbicide-treated areas until all treated plant material is dead and removed. Once the plant populations are controlled, good grazing management can be used to maintain the area in a condition that limits regrowth of the plants (Cheeke, 1998). Large animal enclosures and barns should also be kept free of other potential toxicants, including insecticides, pesticides, petroleum products and medicated feeds. Following label instructions is just as important for large animals as household pets. Medicated feeds, medications and insecticides should be used only on the labeled species. If a pour-on amitraz product intended for cattle is instead used on horses, fatal ileus may result (Gwaltney-Brant, 2004).

Individual Actions

Exposure limiting steps that can be undertaken include those the individual can act on and those that society must take. One can control one's own lifestyle by addressing diet; immediate environment (home and work); avoiding the use of toxic chemical-containing products, avoiding the use of pesticides, avoiding the use of tobacco and tobacco smoke and secondary exposure to smoke, avoiding foods and personal care products that contain phthalates, bisphenol A and lipophilic preservatives such as triclosan, butylated hydroxy anisole (BHA), butylated hydroxy toluene (BHT) and parabens and limiting, to the extent that is medically advisable, the use of lipophilic pharmaceuticals. The individual can also choose to restrict the use of plastics containing phthalates and bisphenol A (Zeliger *et al.*, 2015).

Societal Actions

Steps that society can take include; educational programs and regulatory control of tobacco use, pesticides, persistent organic pollutants, plastics that exude phthalates and BPA and foods and personal care products that contain toxic components such as preservatives and solvents (Zeliger, 2004). The development of green, non-polluting energy can greatly reduce toxic exposures by eliminating the release of lipophilic hydrocarbons, mercury, cadmium and other metals as well as by preventing global warming. Warmer environmental temperatures enhance the volatilization of POPs, pesticides and other organics into the air. Required increase use of pesticides in farming, increase the rates of chemical reactions that lead to higher levels of ozone and secondary air pollutants and increase the risk of wildfires which spew large quantities of polluting species into the air (Noyes *et al.*, 2009).

In Clinical Settings

Obstetricians and gynecologists can serve as a science-based source of guidance on how to avoid potentially adverse exposures. (Solomon *et al.*, 2010) As in other areas of clinical practice, communicating the

science and areas of uncertainties about environmental chemicals can provide patients with the information they need to make informed choices based on the evidence, their values and preferences. Studies related to communicating the results of environmental chemicals in breast milk and other biomarkers lend empirical support to this approach. (Wu *et al.*, 2009).

Pediatricians have long been attuned to the opportunity that clinical practice offers to identify, evaluate and counsel patients about preventing harm from hazardous environmental exposures. The American Academy of Pediatrics has had an environmental health committee for over half a century and publishes a clinicians' handbook for the prevention of childhood diseases linked to environmental exposures. In light of the importance of preconception and prenatal environmental exposures to the health of the pregnancy, and the child and adult that she or he will become, these pediatric approaches to incorporating environmental health into clinical care are equally applicable to reproductive health professionals. Clinicians should intervene as early as possible to prevent exposures during pregnancy by alerting patients to potential hazards and providing guidance on how to avoid toxic exposures. By the first prenatal care visit, disruptions of organogenesis may have already occurred.

Taking an exposure history is a key first step. Clinicians should always ask women of child-bearing age about occupational exposures; the workplace may be an important source of toxic exposures among pregnant women and legal exposure limits for most workplace chemicals are not designed to protect against harm to a pregnancy or the developing fetus. Clinicians should provide anticipatory guidance to all patients with information about how to avoid toxic exposures at home, in the community and at work. Information and resources about environmental hazards can be successfully incorporated into childbirth class course curriculum to help women and men make optimal choices for themselves and their children (Ondeck and Focareta, 2009).

Patient-centered actions can reduce body burdens of toxic chemicals. Research documents that when children's diets change from conventional to organic food, the levels of pesticides in their bodies decline. (Lu *et al.*, 2006) Likewise, recent studies found that avoiding canned food and other dietary sources of BPA can reduce measured levels of the chemical in children and adult family members, (Rudal *et al.*, 2011) and that short-term changes in dietary behavior may significantly decrease exposure to phthalates. (Ji *et al.*, 2010) It is important to recognize, however, that decisions on the individual level about avoiding toxic exposures are complex and often affected by external factors that limit making healthier choices (Adler and

Stewart, 2009). Patient purchasing patterns can also send a signal to the marketplace that can help drive society-wide change. This was demonstrated by the burgeoning market in organic food, (OTA, 2010) the explosion of the market for alternatives to BPA in food contact uses such as baby bottles, (Bailin *et al.*, 2008) and in Walmart's recent banning of a flame retardant found in hundreds of consumer goods from its supply chain. (Layton, 2011).

Many useful resources exist to support clinicians in communicating about environmental risks. (Miller and Solomon, 2003) The Pediatric Environmental Health Specialty Units (PEHSUs) are a network of investigators across the U.S. who support clinical capacity related to environmental health (Trasande *et al.*, 2010) The PEHSUs respond to requests for information throughout North America on prevention, diagnosis, management, and treatment of environmentally-related health effects in children and as such, are poised to serve as a valuable resource for obstetricians and gynecologists in recognition of the inextricable relationship between reproductive and pediatric health.

Specific Toxicity Prevention Strategies Policy Development

The role of clinicians in preventing exposure to environmental toxicants extends beyond the clinic or office setting (Parker, 2011) Society-wide policy actions are essential for reducing toxic exposures to vulnerable populations because many exposures are not controllable on an individual level that is, from air and water. In addition, environmental justice issues related to exposures to toxic substances cannot be sufficiently redressed by individual action. For example, women and men exposed to pesticides at work and in agricultural communities incur substantively higher exposures than the U.S. population overall (CDC, 2007).

There are many examples that demonstrate that clinicians are in an excellent position to take action in policy settings. For example, our industrialized food system is associated with many and varied threats to health, including exposure to pesticides, chemical fertilizers, hormones in beef cattle, antimicrobials in beef cattle, swine and poultry, fossil fuel consumption and climate change, toxic chemicals in food packaging and cookware, and the production and promotion of food that is unhealthy for consumption (Sweton *et al.*, 2011). Policy interventions by the health care sector and clinicians, and patient engagement offer mutually reinforcing opportunities to advance a healthy food system as a strategy to prevent adverse reproductive health impacts (Sweton *et al.*, 2011).

To this end, physician leaders have been instrumental in spurring efforts by health care institutions to support the development of urban

agriculture programs, farmer's markets and local food sourcing outlets to increase accessibility to healthier foods, and healthcare institutions have undertaken procurement policies to create a sustainable and healthy food service model. Nearly 350 hospitals have taken the Healthy Food in Health care pledge in support of these efforts. (HCWH, 2010). Because the food system purchasing power of the healthcare system is so large, about \$12 billion annually. Clinicians becoming engaged in changing their hospital food system procurement patterns can help leverage food system change more broadly. Other examples of institutional policy arenas for clinical action include the reduction of toxic chemicals in healthcare purchasing coupled to bringing policy gaps that impede less toxic procurement patterns to the attention of decision-makers. Clinicians have also been engaged in reducing the use of pesticides in institutional pest-control polices. Clinicians can also work towards policy change in their professional organizations (Raffensperger, 1999). In 2009, the Endocrine Society issued a position paper calling for improved public policy to identify and regulate EDCs, and finding that until such time as conclusive scientific evidence exists to either prove or disprove harmful effects of substances, a precautionary approach should be taken in the formulation of EDC policy.

Regulatory Actions

Regulatory actions may include establishing exposure limits for certain chemicals, setting emission standards for environmental pollutants, or taking protective actions. Protective actions may include: (1) isolation: prohibiting the public from, or advising against, entering certain areas; (2) shielding: using physical shields or protective clothing to prevent exposures; (3) time: limiting the time people may spend in hazardous areas; (4) treatment: treating environmental media to reduce or eliminate toxic or infectious agents; and (5) prevention strategies, such as vaccination against infectious agents or eating antioxidants to prevent toxic effects of certain chemicals (Harper., 2014).

To an increasing degree, environmental management programs are integrating protection of the environment and protection of human health. This may include integrating human health and ecological risk assessments. This also includes integration of effects of pollutants on ecosystem and human health. For example, an algal bloom caused by fertilizer pollution may deplete dissolved oxygen in the water and affect the natural ecosystem, and produce chemicals that are toxic to humans. Such integrated assessments are a practical means of reducing effort and money used in environmental management and protection (Harper, 2014).

Monitoring

In cases where people may be exposed to hazardous agents on a regular basis, environmental surveillance may be carried out. This may consist of regular medical checkups, environmental monitoring, biomonitoring, and dosimetry. Environmental monitoring includes collection of environmental media (air, water, soil) for chemical analysis, or may include real-time monitoring using devices that detect exposures to hazardous agents immediately or nearly so. Biomonitoring includes collection of biological samples, usually fluids or expired air, for determination of chemical concentrations or biomarker analysis (Harper, 2014). Finally, dosimetry is often determined using small devices worn on the person that give an indication of the dose of hazardous agents to which people were exposed. Protecting the public from hazardous agents depends upon knowledge of the health effects of such exposures. One method of gathering information on the health effects of environmental chemicals is by using toxicity tests on animals' (usually rodents) *in vitro* systems (cultured cells or cellular components in flasks or test tubes) (Harper., 2014). A second method of determining health effects of hazardous agents is by clinical challenge studies, clinical observations, and case studies. Challenge studies are when volunteers are exposed to low levels of chemicals or other agents under carefully controlled clinical settings. Clinical observations involve identifying clusters of disease associated with toxic exposures. Case studies are indices where individuals or a small group of people are exposed to high doses of a contaminant as a result of accidental poisonings or industrial accidents (Harper, 2014).

Another tool used by environmental health professionals to determine health effects of environmental agents is the field of epidemiology, which studies the incidence and progression of diseases in populations. Epidemiological studies may be prospective or retrospective. Prospective studies predict the scope and magnitude of diseases that have not yet been manifested, while retrospective studies assess the cause and/or magnitude of disease that had already occurred. Epidemiological studies may also be descriptive or analytical. Descriptive epidemiology uses vital statistics (birth and death rates), patterns of disease, or incidence of disease in exposed and unexposed populations at a single point in time ('cross-sectional' studies). Analytic epidemiology calculates risk factors for hazardous agents by either identifying exposed and unexposed segments of the population and comparing their disease frequencies ('cohort' or 'longitudinal' studies), or by identifying diseased and healthy individuals and determining their exposure histories ('case-control' studies) (Harper, 2014). Another branch of epidemiology is molecular

epidemiology, which incorporates biomarkers into descriptive or analytical studies in order to determine individual susceptibility to environmental hazards. Unfortunately, however, assigning a cause to environmentally induced diseases is often difficult for the following reasons: (1) there is often a latency period of months, years, or decades between exposure and onset of disease; (2) there are often multiple causes of each disease; (3) there are few diseases that are specific to any one agent; and (4) there are usually a host of confounding factors (e.g., age, gender, socioeconomic status, and behavioral factors such as smoking and consumption of caffeine or alcohol) that may influence incidence of disease. For these reasons, epidemiological studies often employ an established set of criteria for establishing causality for any environmental disease. Determination of exposure and toxic effects of chemicals also requires knowledge of toxicokinetics (Harper, 2014). Toxicokinetics is the study of changes in the levels of toxic chemicals and their metabolites over time in various fluids, tissues, and excreta of the body, and determines mathematical relationships to explain these processes. These processes depend upon uptake rates and doses, metabolism, excretion, internal transport, and tissue distribution. Methods for determining these processes include studies with laboratory animals, volunteer human subjects, persons accidentally exposed to high doses of chemicals, and experiments with tissue or organs cultured in the laboratory. Computer simulations of such processes are often formulated using complex mathematical equations. Protection of the public from exposures or effects of chemicals involves constructing safety standards, regulations, and exposure limits. This process usually relies upon human health risk assessment, which is a process of quantifying the likelihood, magnitude, and duration of human health effects from hazardous environmental agents (Harper, 2014). Human health risk assessment of hazardous chemicals consists of the following steps: (1) hazard definition and identification: establishing cause and effect relationships using animal or in vitro toxicity studies, clinical studies, epidemiology, and quantitative structure activity relationships (prediction of a chemical's toxicity from its molecular structure); (2) establishing dose-effect relationships (i.e., what is the magnitude and duration of an effect for a given degree of exposure); (3) exposure assessment includes environmental chemistry and surveillance, mathematical and computer simulation modes of environmental behavior of chemicals, toxicokinetics, and identification of all likely exposure pathways (intentional ingestion of contaminated food or water; accidental ingestion of soil; inhalation of gases, vapors, and particles; and absorption through the skin); and (4) risk characterization, which involves integration of the

above three steps. Like epidemiology, risk assessments may be prospective (or predictive) or retrospective. Prospective studies assess possible occurrence and severity of health risks in which environmental exposure is hypothetical, but likely to occur. In retrospective studies, humans are environmentally or occupationally exposed to hazards and the potential for health risks (and how to mitigate them) is assessed (Harper, 2014). Environmental health professionals, policy makers, and government officials use the outcome of risk assessments for risk communication (informing the public of possible risks and how to avoid them) and risk management (weighing policy alternatives and selecting appropriate regulatory action).

Nutrition

Nutritional intervention has been shown to result in demonstrable improvements in health by lowering the toxicant burden of animals and humans. This was recently illustrated in a case study of a patient who had an extremely high body burden of polychlorinated biphenyls (PCBs) (Redgrave *et al.* 2005). A fat sample obtained by adipose tissue biopsy revealed 3,200 mg/kg Arochlor 1254. This patient also suffered from diabetes and dyslipemia and required daily injections of insulin. Over approximately 2 years of supplemental consumption of foods containing the fat substitute olestra (fatty acid esters of sucrose; approximately 16 g/day in potato crisps), the PCB body burden of the patient's adipose tissue dramatically decreased to 56 mg/kg. At the same time, the elimination of the pollutant directly correlated with the disappearance of the patient's diabetes and normalization of the initial hyperlipidemia. This work, which was also confirmed in animal studies (Jandacek *et al.* 2005), suggests that *a*) a non-absorbable oil phase in the intestine reduces absorption of dietary lipophiles, *b*) a non-absorbable oil phase in the intestine increases the rate of excretion of stored lipophiles that undergo enterohepatic circulation, and *c*) interruption of the enterohepatic circulation can result in clinically meaningful enhancement of excretion of lipophilic compounds.

Another interesting example of effective nutritional intervention is illustrated by the research of Hernandez-Avila *et al.* (2003), who have extensively studied environmental lead pollution as it affects the maternal and fetal health of populations in Mexico (i.e., women who have had moderately high cumulative lifetime exposure to lead). These researchers discovered that calcium supplementation was associated with a marked decrease in blood lead levels (Hernandez-Avila *et al.* 2003), as well as breast-milk lead levels (Ettinger *et al.* 2006) among lactating women over the course of lactation. Furthermore, calcium supplementation during pregnancy decreased maternal blood lead levels and reduced maternal bone resorption. These data

demonstrate that nutritional intervention (e.g., calcium supplementation) may constitute an important secondary prevention effort aimed not only at reducing circulating levels of heavy metals such as lead in the mother but also at reducing lead exposure to the developing fetus and nursing infant.

New technologies, such as the “omics” (molecular imaging, nanotechnology, bioinformatics, etc.), present unique opportunities for understanding the molecular mechanism of disease initiation and the underlying effect of nutrition as a mediator of toxicity. Given the rich experimental information on the relationship between reactive oxygen species (ROS) and dietary antioxidants as it relates to human health, there is strong evidence suggesting that bioactive food components can be introduced for prevention and intervention purposes at points of disease initiation and/or progression of pathways leading to an unhealthy or lethal phenotype [for a recent review, see Seifried *et al.* (2003)]. Unprecedented opportunities exist for the expanded use of nutrition to reduce the risk of disease, and these new enabling technologies would be invaluable in that regard. For example, gene expression studies are providing clues about molecular targets for food components. This may be critical in understanding nutrient/toxicant interactions.

Mediterranean Diet

Reduction of ROS and RNS formation in the body can be readily accomplished through diet adherence to the Mediterranean diet, so named because it is the diet adhered to by populations bordering the Mediterranean Sea. This diet is rich in antioxidant phytochemicals, including phenolics, alkaloids, and nitrogen containing compounds, organo-sulfur compounds, phytosterols and carotenoids. More than 5,000 dietary phytochemicals have been identified in fruits, vegetables, whole grains, legumes, red wine, nuts and vegetable oils. An excellent review of the sources and benefits of dietary phytochemicals is presented by Liu (Liu *et al.*, 2013). In addition to the consumption of foods containing phytochemicals, the Mediterranean diet includes an increase in fish consumption, rich in antioxidant omega fatty acids, and a reduction of red meat consumption, a major source of serum triglycerides in which exogenous lipophiles accumulate (Zeliger *et al.*, 2015). Olive oil, and particularly extra virgin olive oil (EVOO), which is rich in phenolics, is the most representative food of the Mediterranean diet. Tree nuts are another major component of the diet. Both have been shown to reduce inflammation, oxidative stress and lower the risk of developing many ENVDs. These diseases include; Alzheimer's disease, Parkinson's disease, hypertension, diabetes, coronary heart disease and other cardiovascular diseases, obesity various cancers, anxiety and other central nervous system disorders (Liu *et al.*, 2013).

Reduction of Absorption and Formation of reactive oxygen and nitrogen species (ROS/RNS)

Two distinct events must occur for exogenous environmental chemicals to trigger disease: absorption and ROS/ RNS production. Prevention of environmental disease (ENVD) prevalence can be reduced by limiting these events. Research has proven that antioxidants such as kaempferol and ascorbic acids are capable of preventing the formation as well as scavenging for ROS/RNS. Some probiotics as well such as lactobacillus have also proven effective for this purpose when administered appropriately (Zeliger *et al.*, 2015).

The long onset times for ENVDs present opportunities to detoxify and otherwise protect the body of absorbed lipophiles and metals. Sauna has been demonstrated to reduce body levels of lipophilic species and to lead to a relief of disease symptoms (Crinnion *et al.*, 2011). Detoxification by isolating patients in non-polluting environmental chambers along with diet control has been shown to result in reduced blood levels of volatile organic hydrocarbons as well as in the relief of disease symptoms (Rea *et al.*, 1996). Heavy metals can be removed via chelation by dietary components. Vitamins B1, B6, C and E have been shown to chelate heavy metals, as have garlic, ginger, onion, green tea, curry, tomatoes and other foods (Zhai *et al.*, 2015). Selenium is an essential metal in the human body. When ingested in its selenite oxidation state, it has been shown to protect against metal induced neurotoxicity, renal toxicity and various cancers (Li *et al.*, 2013).

Body Protective Defenses: Metabolism and Elimination

The human body naturally metabolizes and excretes exogenous toxic chemicals. Volatile and semi-volatile organic compounds are readily metabolized and eliminated. Though persistent organic pollutants, such as Polychlorinated biphenyls (PCB) polybrominated diphenyl ethers (PBDEs) and biphenyls (PBBs), dioxins and furans are retained in adipose tissue for decades (Yu *et al.*, 2011), they slowly but continually partition into the blood stream from whence they can be absorbed by polyunsaturated oils, such as olive oil, and excreted (Milbrath *et al.*, 2009). Metals are also eliminated naturally via the action of natural chelating agents contained in spices, tea and other foods, for example (Mandel, 2006). In addition, the body has the ability to adapt to and repair damage caused by toxic chemicals (Rea, 1992). These factors delay the onset of environmental disease. The liver and kidneys play vital roles in metabolism and elimination of toxic chemicals.

Limitations to Toxicity Prevention

The measures to prevent ENVDs just discussed cannot always be implemented. Ignorance, socioeconomic status, lifestyle, peer pressure and economic interests of chemical manufacturers and

polluters act counteractively to prevent the limiting of chemical exposures and ROS and RNS formation. There are also conflicting situations where well-meaning people on both sides of an issue can reasonably disagree. Two examples of such situations serve to illustrate this point. DDT and its metabolite DDE are persistent organic pollutants that are causative of the ENVDs. DDT, however, is still being used in parts of the world to control mosquitoes that carry malaria and other infectious diseases (Sahu *et al.*, 2014). Water is routinely disinfected with chlorine and thus spares millions of people from exposures to water-borne pathogens. Yet, the chlorinated and brominated hydrocarbon, haloketone and haloacetic acid byproducts of chlorination are human toxins (Tardiff *et al.*, 2006). These examples illustrate the often difficult choices that need to be made with regard to the use and subsequent human exposures to toxic chemicals (Zeliger *et al.*, 2015).

Conclusion

Regulatory agencies have assigned acceptable levels of exposure, known as permissible exposure levels (PELs), time-weighted averages for 8 hours of exposure (TWAs) and no-observed-effect concentration values (NOECs) at which exposures presumably have no toxic effects. Many pollutants, such as heavy metals and persistent organics, bioaccumulate in the body, and remediation strategies to remove these chemicals from the environment are extremely difficult and capital-intensive. Exposure of animals to concentrations of toxic chemicals beyond the minimum permissible exposure level induces deleterious health effects including terminal malignancies. Therefore, strategies that modulate the effect of toxicants on pathophysiologic processes involved in disease etiology and progression are essential to public health. All stakeholders including clients, clinicians, nutritionists, policy makers and regulatory agencies must have their hands on deck to ensure effective surveillance and monitoring to prevent toxicity especially in high-risk populations.

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