"Hormesis"—An Inappropriate Extrapolation from the Specific to the Universal

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Although it is generally accepted that some chemicals may have beneficial effects at low doses, incorporating these effects into risk assessments generally ignores well-established factors related to exposure and human susceptibility. The authors argue against indiscriminate application of hormesis in assessments of chemical risks for regulatory purposes. *Key words*: hormesis; risk assessment.

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There is no debate that under some circumstances low doses of essential micronutrients can be beneficial, while they are toxic at higher doses. Some have argued that this phenomenon should be generalized to all chemicals, including those for which we have no evidence of positive health benefits. The phenomenon of adaptive health effects at low doses has been termed "hormesis." Some proponents of this concept suggest that it should be considered the norm, rather than the exception, and applies to all toxicants, in the absence of evidence to the contrary. However, the data on which this concept rests do not indicate that it is either universally adaptive or widespread. Moreover, even if it is accepted that some chemicals may have beneficial effects at low doses, incorporating these effects into risk assessments generally ignores critical well-established factors related to exposure and human susceptibility.

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Current regulatory approaches rest on the assumption of low-dose linearity, whereby compounds found to be toxic at higher doses are assumed to have similar properties at lower doses. If hormesis were a general rule, then it is argued that the dominant approach to setting standards for toxic chemicals should be changed.[1–4] This conclusion is based on a restricted reanalysis of toxicology literature and ignores one fundamental limitation of modern toxicology research: most experimental studies investigate genetically homogenous and mature animals. As a result, the sensitivity of the developing organism in a heterogenous population with varying nutritional and health status cannot be estimated based on available toxicology data.

As the scientific study of poisons, toxicology remains a descriptive, quantitative, and experimental science that details the biological consequences of exposures to toxins. In pharmacology and toxicology, adult, purebred animals are studied in order to simplify generalizations, but their use also limits deductions that can be broadly drawn. In an effort to clarify recent discussions of the issue, the concept of hormesis is reviewed here in the context of developmental and comparative toxicology and epidemiology.

To be sure, dose makes the poison—so goes the oft-repeated observation of the sixteenth-century progenitor of modern pharmacology, Theophrastus Paracelsus. As the science of toxicology has matured, it has become clear that dose is not a simple concept. Thus, *when* exposures take place, along with *the rate* at which dose is absorbed, ***concurrent exposure to other chemicals,*** and the pre-existing *nutritional and health status* of the animals can be even more important than the total quantity of dose in determining the biological importance of any given exposure.

Several recent reports have argued that since some low-level exposures to micronutrients can be beneficial, while at higher doses they are toxic, carcinogenic, or teratogenic, this calls for a fundamental shift in environmental policy to treat higher levels of pollutant exposures as safe. This position lacks scientific merit and fundamentally ignores basic findings in toxicology and epidemiology.

The suggestion that "beneficial" hormetic responses should be incorporated into risk assessment disregards several well-established principles that underpin a public-health-protective approach to regulating expo-

sures to toxic substances: 1) Susceptibility varies over the course of a lifetime and in many cases timing of exposure can be more important than dose in determining health outcomes; 2) Individual responses range from exquisite vulnerability to insensitivity stemming from genetic heterogeneity and differences in health status; and 3) Exposures in the real world do not occur to single substances, but to mixtures of toxicants that can interact with nutritional and other host conditions. Moreover, many compounds affect the same target tissues by similar mechanisms or modes of toxicity. The mixtures of chemicals any individual is exposed to vary depending on the nature of his or her work, the indoor home environment, drinking water supply, food sources, where the individual attends school, and socialization, in addition to lifestyle choices such as hobbies, sports, hygiene, and other factors.

At its most basic level, a hormetic response is characterized by low-dose stimulation and high-dose inhibition.[2] If the definition of hormesis ended here there would be little controversy. After all, biphasic dose–response relationships of this nature have been reported frequently in the peer-reviewed literature.[5] However, a more selective and increasingly cited definition of hormesis considers the phenomenon to be an adaptive and universal response.[6] Supporters of this definition advocate that the approach to setting standards for controlling and cleaning up environmental pollutants needs to be changed,[2,7,8] and they argue that the default assumption, in the absence of contradictory information for regulatory purposes, should be that at very low doses, exposure to chemicals has a "stimulant" effect, and that this is a positive effect in the majority of cases.[2] They state that taking this approach to regulation will optimize beneficial effects while preventing toxic responses.[7,9] This position ignores substantial and compelling literature on several pollutants frequently cited as models of this alleged beneficial dynamic of low doses: certain heavy metals and TCDD.

A number of lines of evidence indicate that mercury, zinc, and other heavy metal pollutants do not have beneficial effects at environmentally relevant levels when the totality of toxicologic and epidemiologic evidence is considered. One of the most widely cited examples of evidence that hormesis may occur is inappropriately taken from a 1978 two-year chronic toxicity and carcinogenicity study of TCDD (dioxin).[10] The apparent hormetic response drawn from this study is largely an artifact of the evaluation methods applied by the proponents of hormesis. In this study, in no case was an individual tumor response non-monotonic. But by calculating the total number of tumors, an impression can be created that the overall tumor response was hormetic. In fact, none of the specific tumor responses can be considered non-monotonic. Relying on the questionable aggregation of all tumors, this analysis reported decreased tumor incidence and "no effects considered to be of any toxicological significance" at 0.001 μg/kg/day (~22 parts per trillion (ppt) in the diet and 540 ppt TCDD in terminal fat samples). In fact, other experimental studies have found that these same levels of exposure are associated with a range of adverse effects in primates.[11]

Cadmium is another heavy metal that has been specifically discussed as a model hormetic agent because low doses have been shown to reduce tumors in some species and increase growth in several varieties of plants.[2] However, two recent epidemiology studies have linked current cadmium exposures with adverse health outcomes. Thus, investigation of a sample of more than 8,700 adults found that urinary levels of cadmium in the general population are positively associated with impaired fasting glucose (prediabetes) and diabetes after adjusting for age, ethnicity, sex, and body mass index.[12] This finding is consistent with data from laboratory animals showing that cadmium damages the pancreas and alters glucose regulation.[13–15] Cadmium and many other heavy metals are also fundamentally toxic to the kidneys,[16] with chronic low-level exposure leading to tubular damage.

Ethanol is sometimes referred to as a classic hormetic agent because low or moderate drinking is associated with reduced mortality, while alcoholism is clearly tied to increased mortality and morbidity. This beneficial effect of moderate drinking may be true for nonpregnant women, when defined as 1.2 to 2.2 drinks per day, but even small amounts of alcohol during pregnancy (0.5 drinks per day) have been associated with adverse behavioral and developmental outcomes in children, including aggressive behavior.[17] Because a clear threshold for this risk from drinking during pregnancy has not been established, the American Academy of Pediatrics and the American College of Obstetrics and Gynecology recommend abstinence for women prior to conception and throughout pregnancy.[18] Further, ethanol ingestion is also associated with increased risks of breast cancer in women who drink regularly[19]

There are many reasons that fetuses, infants, and children are more sensitive to many chemicals than adults. These range from the well-known susceptibilities of the developing nervous system to neurotoxins such as lead[20] and mercury[21] to the less well-known age-related differences in elimination. A comparison of 45 different pharmaceuticals found that half-lives are three to nine times longer in neonates than in adults, depending on the chemical's primary elimination pathway (e.g., CYP or P450, glucuronidation, renal, other non-CYP elimination pathways).[22] The physiologic heterogeneity in this case of retention is also critically important, because averages can mask significant differences and underestimate the much more substantial impact exposures will have on some individuals. Approximately 7% (6/85) of 1-week- (< 7 days) to 2-month-old babies had an elimination half-life more than ten times longer than the adult average level.[23]

Only 1% (1/85) of the 1-week- to 2-month-old infants had a faster half-life than the adult average value.

Both age-related and genetic variability affect the toxicity of the very common family of pesticides, organophosphates (OPs), that are present in food and pet treatments. The OPs and their sister pesticides comprise the majority of cholinesterase inhibitors that are offered by the hormesis proponents as examples of chemicals that may be beneficial at low doses. However, the hormesis promoters do not discuss the serious consequences of variations in susceptibility to these pesticides that arise from differences in basic physiology, age, metabolism, and concurrent exposures to other chemicals. The enzyme paraoxonase (PON) is essential to metabolize toxic breakdown products of OPs. People with higher than average PON levels due to genetic polymorphisms metabolize OPs more quickly.[24] Infants, who do not produce adult levels of PON until approximately age 2, are especially vulnerable to OPs.[25,26] Alcohol consumption, cigarette smoking, and certain medications also impact PON-1 activity.[27,28] Similarly, activity of another enzyme important in OP detoxification, malaoxonase, varies sevenfold within humans—and this number does not begin to include differences between adults and children.[29] This degree of variation is not addressed by the default factor of 3.2-fold that was used to account for pharmacokinetic variability in risk assessment.[30]

Some of the assumptions of hormesis appear contradictory. Thus, Calabrese maintains that maximal low-dose hormetic response (stimulation) occurs on average at a dose fivefold below the "no observed adverse effect level" (NOAEL).[1] If this were the case, then simultaneous exposure to five or more compounds that are equally potent in eliciting a given response, each at a level one fifth of the NOAEL, would be enough to move an organism from the low-dose potentially "beneficial" range, to the range where adverse effects are expected. Given that residues of hundreds of chemicals can be measured in humans,[31–35] many affecting the same tissues and fluctuating in concentration over the course of a lifetime, trying to titrate exposure to achieve a relatively narrow hormetic range is untenable.

Some recent epidemiologic studies have found that the marginal impact of pollutants is far greater at lower doses than at higher ones. In a panel study of children from Rochester, New York, Canfield et al.[36] found that blood lead concentration was inversely and significantly associated with reduced IQ in the first five years of life. When estimated in a nonlinear model, IQ declined by 7.4 points as lifetime average blood lead concentrations increased 1–10 μg per deciliter, and declined by 4.6 points as lifetime levels averaged 10–20 μg/dL. Thus, per unit of exposure, the impact of lead on I.Q. was marginally greater at lower levels of exposure than at higher levels.

Modern pharmaceutical development is based on the realization that if a toxic agent is found to have a truly beneficial effect, and there are not other less toxic materials available, then it should be administered as a therapeutic drug. But, the notion that such an approach can be applied to environmental exposures is without merit. Even for pharmaceuticals, it is understood that there are tradeoffs between benefits and risks and between risks and risks. For example, although aspirin is a generally well-tolerated pain reliever and is increasingly advocated as a preventive tool to reduce the risks of heart attacks, stroke, and colorectal cancer,[37,38] it is also linked to increased risks of gastrointestinal bleeding, cerebral hemorrhage,[38] and asthma attacks.[39] In addition, aspirin is not recommended for children or teenagers who have, or are recovering from, chickenpox or flu-like symptoms because it can cause debilitating and sometimes lethal Reyes' syndrome.[40] Some toxicants have been shown to be effective against advanced disease. For instance, the well-known teratogen thalidomide reduces oral ulcers in HIV patients and slows the progress of multiple myeloma.[41]

For a number of reasons, pharmaceuticals are treated differently from toxicants. Drugs are given and taken based on formally established rules requiring that manufacturers and health professionals obtain informed consent from patients regarding potential side effects and benefits. With toxic pollutants, the public is not provided such routine information about the balance between the risks and benefits that may arise, nor are they given the ability to make choices about their exposures. Consider the difference between one of the most widely prescribe pharmaceuticals used to treat breast cancer, tamoxifen, as compared with xenoestrogenic pollutants, such as some plastics, fuels, and volatile organic agents.[42] Tamoxifen is a hormonally active drug used to prevent primary or recurrent breast cancer. In a small percentage of women, tamoxifen causes deep vein thrombosis, stroke, uterine hyperplasia, and, less often, uterine cancer, and rarely uterine sarcoma, with no way to determine who will have these adverse responses. The FDA Fact Sheet on tamoxifen states:

> It is very important that the public and physicians be given accurate information on potential risk so they have the information to weigh the benefits versus the risks of using tamoxifen.[43]

By law these risks are explained to women by their physicians, with information provided in writing with the medication. The analogous situation does not exist with widely used estrogenic materials in the environment, which carry no formal warnings that they may be transformed into hormonally-mediated carcinogens. In fact, most women do not know they are being exposed to estrogenically-active compounds when they use common household products, use personal care prod-

ucts, or are otherwise exposed to endocrine-disrupting materials in their workplaces or in the ambient air, food, or water.[44]

Regarding the potential policy implications of adopting "hormesis" as a guiding concept for regulatory purposes, Texas Institute for Advancement of Chemical Technology (TIACT) at Texas A&M,[8] a "non-profit, charitable organization dedicated to the advancement of chemical technology through an informed public" (supported by donations from Dow, BASF, Bayer, Shell Chemical Company, and Syngenta), argues:

> The scientific acceptance of hormesis with its possible benefits at low-level exposure could come at no better time than the present when environmentalists and others are calling for bans on more and more chemicals, such as *chlorinated hydrocarbons* [emphasis added] to prevent low-level exposures. Furthermore, the *low-exposure paradigm* [emphasis in original] would make it possible for society to enjoy, safely, the benefits of many chemicals that have been banned in the past or could be banned in the future" [page 1 of the executive summary][45]

While "beneficial" hormetic effects can occur in some instances, it is indeed rare that exposures to toxic chemicals, even at low exposure levels, are without some risk in others. Despite powerful interests pressing for the incorporation of hormesis into regulatory policy, the concept does not rest on well-established universal principles. This brief review has indicated that scientific evidence developed over the past four decades does not support a universal extension of the concept of hormesis to regulatory policy.

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