Low-Dose Toxicology

*Narratives from the Science-Transcience Interface*

Sheldon Krimsky

Uncertainties associated with low-dose exposures to chemicals that are known to be hazardous at high doses were probably being raised at the dawn of human civilization when Homo sapiens began distinguishing among edible, near edible, and poisonous plants. The study of toxicology began around the sixteenth century with the writings of an Austrian physician and contemporary of Leonardo da Vinci, named Philip von Hohenheim, who practiced “chemical medicine.” Hohenheim is more popularly known as Paracelsus, a name he adopted to elevate him above a prominent Roman physician named Celsus. Paracelsus is known to have said: “All things are poison and nothing is without poison, only the dose permits something not to be poisonous.” He believed that low doses of a poison could be used to cure diseases brought about by the poison (“like cures like”) (Borzelleca 2000). By the twentieth century, when toxicology had become a scientific discipline, the observations that low doses of a poison can be therapeutic became epitomized by the aphorism “the dose makes the poison.”

Modern toxicology is a battleground of contested issues pertaining to low-dose exposures. The domain of published work contains a number of presuppositions, some false, some true, and some indeterminate. The core questions underlying the low-dose narratives are: (1) Are there empirical tests that can be used to evaluate the human health effects of exposures to extremely low doses of a substance? (2) Are there methods that can be used to generate a reliable dose-response curve for extremely low doses of a substance? and (3) How can we know and with what level of confidence whether a chemical below a testable dose is safe?

I approach this subject by treating the controversy over low-dose exposures as a confluence of alternative narratives. Each narrative may frame the problem differently and builds its argument or draws its conclusions from empirical evidence based on a preferred set of presuppositions, which may not be empirically verifiable or falsifiable. In this respect, rather than being in direct
conflict, some of the narratives may be orthogonal to one another, like two religions whose adherents speak a different language, preach from different texts, and hold a different world view. The chapter is structured as follows. First, six guiding presuppositions that provide the framing assumptions for the low-dose narratives are identified. These framing presuppositions are themselves contested and therefore help to explain the differences in how scientists approach low-dose effects. Then, three modalities of evidence used to obtain answers to low-dose human health effects are examined. They are: direct empirical evidence; indirect empirical evidence, and theoretical evidence. Next, I explain how the gene-environment interaction model of disease complicates efforts to assess low-dose health effects.

I go on to examine the classic problem of the linear dose response curve for extremely low doses, including the reproducibility of low-dose effects. Next, a case study of Bisphenol A (BPA) reveals competing narratives of low-dose effects impeding efforts to reach a consensus position. Finally, I argue that the path of mechanistic reductionism, which largely defines the approach used by some of the narratives in toxicology, is not the best approach for regulating the health risks of low doses of toxic chemicals. Further, my approach using competing narratives helps explain why acquiring more data often fails to resolve the issue of when low-dose exposures become a health risk deserving of regulatory action.

**Narrative Frames on Low-Dose Effects**

One cannot read the scientific literature on low-dose toxicology without experiencing the contrasting narratives of this field. There is nothing about low-dose toxicology that is common across all chemicals, consistent across all modes of action, or predictable across all genotypes. I shall begin my inquiry by exploring several of the framing presuppositions that have become a notable part of the scientific literatures:

A. The human effects of extremely low doses of chemicals are beyond what can be learned from direct observation. One must introduce a priori (empirically unverifiable) assumptions to extrapolate from the effects of high doses to low doses of a chemical substance. These assumptions take the form of dose response curves extrapolated from points in the high-dose range or of thresholds below which there are no effects (NOEL = No Observable Effect Level).

B. There are discontinuities between the effects of chemicals at high and low doses, sometimes referred to as non-monotonic, making simple linear extrapolation unrealistic.
C. Multiple and differentiated physiological mechanisms operating in mammalian systems can make the determination of a simple dose response relationship for a single chemical, and a single outcome over low- to high-dose range, highly unrealistic.

D. Low-dose studies are difficult to replicate because they are vulnerable to sensitive stochastic effects. The analogy is the “baking effect.” Even though the baker uses all the same ingredients in a precise order, with a standardized baking process, the outcome may vary significantly by virtue of a small number of stochastic effects.

E. Embryos at particular windows of development (the first trimester) are more sensitive to low-dose effects than more developed fetuses and adult organisms.

F. Epigenetics has introduced the idea that the embryo may have been affected by the mother or grandmother’s exposure to low doses of chemicals. Something in the organism’s external environment alters how a gene is expressed without changing the structure of the gene. This model is akin to “action at a distance.” In this case it is a generational distance. The mechanisms proposed to explain such effects are attributed to a combination of “genetic switches” and “imprinting” of the genome, one of the newest and least-studied mechanisms for low-dose effects.

These presuppositions are found throughout the low-dose literature and have become subjects of intense debate and the source of policy conflicts. In some instances, these debates have helped to paralyze regulatory bodies, preventing them from reaching a conclusion on specific toxic substances. Beyond these presuppositions, there are also three epistemic modalities used in science to acquire evidence and reach conclusions on low-dose effects of chemicals. The combination of the presuppositions and the epistemic modalities contribute to a particular narrative.

Epistemic Considerations in Regulating Low-Dose Effects

Regulators have always had difficulty in determining acceptable levels of a substance at low doses. They are expected to show evidence that low doses of a substance are harmful before they can restrict or ban its use. In drug development, manufacturers are required to demonstrate both efficacy and safety before a drug is approved for consumers. For all chemicals that do not have therapeutic use, the burden is on government to show that it is unsafe. Of course, regulators can ask for data from manufacturers if they have prima facie evidence that a substance may be harmful. But the manufacturers are only expected to provide data that they can easily obtain. And here lies the problem
for low doses. There are methodological problems in obtaining evidence in support of the hypothesis that the substance is harmful at low doses. And as the aphorism goes, “No evidence of a chemical risk is not evidence of no risk.” This is particularly true when there are impediments to obtaining data.

A great number of claims, misunderstandings, and some myths have been raised about low doses. It is sometimes said that there can be no direct empirical evidence for low-dose effects and that all evidence must come from animals where extrapolations are made from high doses. It is also said that effects found in animals in relatively short-lived species such as the rat or mouse cannot be used to estimate the effects in a long-lived species such as humans. Believers in hormesis argue that some industrial chemicals that are known to be toxic at high doses are beneficial at low doses (Calabrese and Baldwin 2002). Others maintain that we cannot find a causal relationship at low doses because there can be no statistical verification of low-dose extrapolation (Pesch et al. 2009), where a variety of shapes of curves may all fit (Armitage 1982: 126).

There are three general methods, which I refer to as epistemic modalities, that are used to acquire information about low-dose effects of substances on humans. They are: direct evidence, mainly epidemiological studies on humans; indirect evidence by extrapolation from high and moderate doses to low doses or from animal studies to humans; and theoretical approaches that apply mechanistic modeling. Each method has its unique benefits and limitations.

Direct Evidence

Epidemiological studies of large human populations exposed to low doses of a substance can sometimes yield reliable evidence of health effects. The data can come from chemical spills or radiation exposure (Pierce and Preston 2000), where the doses of exposure are well understood or measured. To get low-dose data from animals in traditional toxicological studies that are statistically meaningful could require hundreds to thousands of animals because animals do not live that long. When oncogenic-sensitive mice were developed, low doses could be used in conjunction with smaller sample sizes. Critics of such experiments argue that the animals are so artificial that their effects cannot be used to shape policies about human disease.

Endocrine disruptors (industrial chemicals that behave like human hormones) present a different model for studying the effects of chemicals on the developing organism. Very low doses of toxicants can produce statistically reliable, observable effects with far less than 100 mice. Extrapolation is not required. Moreover, high doses of the same substances may not exhibit the same effects.
Many studies involving the impact of toxicants on the endocrine system use 6–12 mice in the experimental sample and the same in controls (Salazar et al. 2006).

**Indirect Evidence**

The most common method of acquiring data for low-dose effects of chemicals is through extrapolation from high doses in animal studies or from occupational data involving human exposure. This has generated debates over the shape of the dose response curves prompting some scientists to claim that the method of extrapolation introduces subjective judgments about how chemicals will respond at low doses. In addition, after deciding which extrapolation model to use, and then extrapolating down to a regulatory “safe” level, for endocrine disruptors there are effects at concentrations several orders of magnitude below the “safe” level.

**Theoretical Approaches**

The use of mechanistic modeling to obtain low-dose toxicity information is growing in interest (Rietjens and Alink 2006: 980). Among its benefits is that it is grounded in identifying the “mechanism of action” of a specific chemical, including its biochemical pathways, and measurable endpoint effects. This means that society does not regulate a chemical until the mechanism of action is fully determined, for each endpoint, for each chemical present, for each organ, and for each strain of animals. The bar of scientific knowledge required for mechanistic modeling can be much higher than that for indirect evidence and, where available, direct evidence.

One of the most complex problems in public health is how to regulate substances that are known to cause cancer in animals, or at least some species of animals, but for which there is not direct evidence that they cause cancer in humans. For many years regulators assumed that there was no safe dose of a carcinogen. That was the premise behind the U.S. Delaney Clause of the 1958 Food, Drug, and Cosmetic Act. The complexity of regulating carcinogens mirrors the complexity of the mechanisms underlying cancer. It has been often said that cancer is not one disease but many diseases under the same name. Some cancers have a long latency period from the point of exposure. Moreover, the etiology of cancer is a multistage process and each stage provides necessary but not sufficient conditions for a particular cancer to develop. Other theories of cancer etiology influence the way we think about low-dose carcinogens. These include the idea that cancer is a breakdown of the immune system or a malfunctioning of the signaling that takes place between cells of
different tissues. One of the most important new theories is based on the link between genes and the environment.

**Gene-Environment Interactions: The No-Effect Outcome**

While many assumed there was no safe dose of a carcinogen, it is difficult to understand how, in some cases, low doses of a carcinogen may be more lethal than high doses. Some studies have shown that the risk of lung cancer associated with smoking and a particular polymorphism is greater at lower doses of cigarette smoke than at high doses. It is hypothesized that the genetic susceptibility to cancer (in a gene-environment interaction) may be more responsive at low doses because “from a metabolic point of view... at high dose levels the relevant enzyme is saturated both in rapid and in slow metabolizers, while this does not happen at low doses” (Vineis 1997: 1). Thus, at high dose levels of a cigarette carcinogen, critical enzymes that are part of the cancer etiology are disabled, but become active at low levels. Another hypothesis is that one must look at the “carcinogen” in its context of use. For example, at low doses, mixtures, including chemicals in one's diet, “might prove to be more important than exposure to single agents” (Vineis 1997: 3). Variations in peoples' genetic susceptibility to chemical diseases may skew linear dose response curves, making the risk of contracting cancer higher than expected.

At very low doses, the chemicals may reside in certain regions of the body that are more susceptible to organ damage or oncogenic effects. Gerde (2005: 145) notes: “While the overall dose of inhaled substances can be reasonably measured and assessed, the local dose to disease-prone regions of the respiratory tract is often impossible to measure directly.”

Another complexity in low-dose assessment of chemical hazards is that some individuals have different metabolic genes (polymorphisms) that encode enzymes that are involved in the metabolism of carcinogenic agents. People with different metabolic polymorphisms may have higher or lower risk of cancer when exposed to certain chemicals. Not everyone reacts to low doses in the same way. There are gene-environment interactions at work. Without understanding the genetic factors, studies may obscure the low-dose effects of chemicals (Taioli and Garte 1999).

Consider an experimental design involving two groups of people as in a case control study. Study Group I is the experimental group and Study Group II is the control (see Figure 11.1).

Suppose we cluster all the people in whom we see an effect into Group I. People with similar characteristics but without an effect are clustered into Group II. We then examine the individuals in Group I to see if there is a cor-
relation between environmental contaminant C and the people who have the effect. Then we determine whether the contaminant correlates with the people in Group II. The true cause of the effect is: \( A_1 + B + C \rightarrow \text{Effect} \). \( A_1 \) is a genetic factor (polymorphism) and B is a social component, constant for both groups. In Group II we have: \( A_2 + B + C \rightarrow \text{No Effect} \). The environmental factor C does not show up any more strongly for Group I than it does for Group II. Without knowing about the existence of the polymorphisms, one might conclude that C is not the cause of the effect. In fact, C is a necessary condition, but requires both \( A_1 \) and B for its effect. Without understanding gene-environment interactions, case control studies may not reveal low-dose effects. This could help explain the negative results in case control studies of adult women with breast cancer on whether DDT or PCBs could be a contributing cause.\(^1\)

Another explanation that can account for a no-effect outcome in case control studies of low-dose exposure of persons to endocrine-active chemicals is that such studies neglect the stage of development during which the exposure took place—the “window of exposure.” Chemicals may affect embryos and fetuses differently than they do adults. “Data from studies with adult animals thus cannot be used to predict the pharmacokinetics of chemicals in pregnant females and fetuses” (Welshons et al. 2003: 1001). One study compared women exposed to DDT before the age of fourteen with women exposed after that age. The investigators found a fivefold increased risk of breast cancer among women who were first exposed to DDT before the age of fourteen in around 1945, when DDT came into widespread use. Women who were not exposed to DDT before age fourteen did not have a higher risk of breast cancer (Cohn et al. 2007). Given the uncertainties around low-dose exposures, when no direct evidence is available, scientists have made two bold assumptions: that the dose response curve is linear and that there are no thresholds at low doses.
**The Linear, Non-Threshold Default Position**

The default model for chemical carcinogens and radiation has been the assumption of a linear non-threshold (LNT) effect. When first adopted, it was based on the assumption that a single mutation can launch the cell into becoming a cancer cell. But today the onset of cellular carcinogenesis is considered more complex than the “one-hit” hypothesis. There are cell repair mechanisms that can respond to mutagenesis before carcinogenesis takes hold. Moreover, mutations are required in more than a single cell. Traditionally, regulatory bodies adopted a two-tiered approach to low-dose extrapolation. The LNT was applied to carcinogens and the NLT approach was used for chemicals that exhibited noncancer effects. However, the dichotomy is losing its force among toxicologists in favor of more reductionist approaches that look at “mechanisms of toxicity” that are purported to reveal more information about low-dose effects. Mechanism of Action (MOA) after all requires a more detailed understanding of biological events at the molecular level. Once the toxicological approach for low-dose extrapolation turns to mechanism of action, you must have models that require validation with more levels of complexity than simply linear extrapolation. And when there is a dearth of good data to validate the mechanistic models, regulatory decision making is put on hold. Good data are exactly what is missing in the low-dose range. Some scientists advocate using the LNT assumption unless there is sufficient justification to accept the MOA model. However, once MOA is sought as the gold standard, commercial interests may hold it up as the desired standard for regulation, possibly slowing down any progress in regulating new chemicals.

Increasingly scientists are questioning the dichotomy between cancer and noncancer outcomes in low-dose extrapolations of exposures of chemicals and radiation. One of the findings of a 2007 EPA and Johns Hopkins Workshop was: “The historical dichotomy between low dose response extrapolation methods (typically applied to cancer and non cancer outcomes) should be set aside.” Their findings state that the emphasis should be placed on low-dose extrapolation models informed by the mechanisms of toxicity.

**The Adaptive Response**

Health physicists have been studying low-dose radiation since the aftermath of World War II. One of the unexpected outcomes of these studies is the adaptive response to low-level radiation, which confounds the conventional wisdom that has embraced the LNT view of radiation effects. Scientists studying the effects of ionizing radiation on human lymphocytes found that, compared to nonirradiated cells, low-level radiation provided more protection to high doses
of ionizing radiation and chemical mutagens (S. Wolff et al. 1988). Cai (1999) noted that “Adaptive response (AR) induced by low-dose radiation (LDR) … is the induction of cellular resistance to genotoxic effects caused by subsequently high-dose radiation (HDR).” It is hypothesized that the low-level ionizing radiation boosts the repair mechanism of cells (antioxidant activity) preparing them for mutagens (radiation or chemicals). The system of cells is being viewed as analogous to an immune system, which, by being exposed to certain proteins, can be activated to fight against viruses and bacteria. The visualization of the cells and DNA as an “immune-like” system could revolutionize health physics and toxicology and open the door for a hormesis-like theory of radiation (hormesis is the theory that low doses of substances that are toxic at high doses may be beneficial to human health). Some scientists are applying the same idea to low doses of chemicals without using the term “hormesis.” In addition, they are using the “drug framework” for industrial chemicals. Recognized as having both positive and negative effects, drugs are approved when it is found that the positive effects outweigh the negative effects. Here’s how one group of scientists views the assessment of low-dose exposures of industrial chemicals under the “drug framework”: “the biological effects at low levels of exposure not only may be adverse but also can be beneficial depending on the target organ, the actual endpoint studied, the receptors activated, and/or the gene expression, protein and metabolite patterns affected” (Rietjens and Alink 2006: 977). They argue that toxicologists “should redirect their focus from looking at adverse effects only to also characterizing the beneficial effects, including even the beneficial effects of supposed adverse effects” (Rietjens and Alink 2006: 980). A recent example of a claim of “adaptive response” is the report that cell phone radiation reduces Alzheimer’s disease in mice.3 A good example of an emerging narrative framework for endocrine disruptors can be found in the case of Bisphenol A.

**Low-Dose Exposures to Bisphenol A**

Bisphenol A (BPA) was first reported to be synthesized in 1891 by the Russian chemist Aleksandr P. Dianin (1851–1918) (Dianin 1891; 1914; Rubin and Soto 2009). He prepared BPA from a condensation of acetone, which is how it got the suffix “A.” Its estrogenic properties were discovered by Dodds and Lawson in 1938 by tests on ovariectomized rats. BPA was manufactured in the late 1930s, when it had been introduced extensively in consumer products. Toxicological data were reported decades ago and a No Observed Effect Level (NOEL) was established in animal studies. But since the discovery of endocrine-disrupting chemicals in the mid 1990s, BPA was studied at much lower concentrations. The reason it was studied at concentrations far below what was
considered an acceptable dose was that a new mechanism of interaction was introduced. The mechanism involved estrogen receptors. Chemicals can bind to the receptors, which are either inside or on the cell surface, and disturb the normal endocrine system by “mimicking, modulating, or antagonizing” (McLachlan 2001) the pathway of an endogenous hormone. This mechanism was first discovered for estrogen receptors, but soon was extended to many other hormone systems.

Most NOELs are determined by adult exposures. But scientists have recently distinguished between the effects of chemicals on embryos and fetuses (in pregnant women) and adults. Hormones in development operate at particular time windows. Very small changes in hormone levels at a particular time of development may have dramatic effects on the organism, possibly at some later time. A two-tier system of toxicology is in the making, reflecting independent operating mechanisms. The traditional toxicological range was seldom fifty times below the Maximum Tolerable Dose (MTD) in animals. The MTD for BPA is 1,000 mg/kg/day. The EPA’s lowest observed effect level (LOEL) is 50 mg/kg/day. The Reference Dose (RfD) of Bisphenol A based on a safety factor of 1,000 was calculated to be 50 µg/kg/day.

Low doses of endocrine-disrupting chemicals (EDCs) were tested on another set of toxicological assumptions—namely, that EDCs have the greatest impact when exposure occurs during development. During embryonic and fetal development, “endogenous hormones regulate the differentiation and growth of cells, and developmental processes appear to have evolved to be exquisitely sensitive to changes in hormone concentrations. … Even in animals that are genetically identical, small fluctuations in endogenous hormonal signals during development provide the basis for significant variability in phenotype” (Welshons et al. 2003: 995). Because EDC compounds fall into different mechanistic models than traditional toxicants, high-to-low-dose extrapolations cannot be used. The assumptions of threshold values, monotonic dose response curves, and singular dose response curves do not map reality. The mechanism of action of most toxicants is unknown (Welshons et al. 2003: 995). The endpoints, such as tumors or liver toxicity, are measured without understanding the pathways leading to the pathology (Hanahan and Weinberg 2000). With EDCs, scientists are continuing to work out the mechanistic pathways. Three main problems with traditional toxicological approaches applied to EDCs are: (1) they operate with only one macro-endpoint and assume a single mechanism of action; (2) they do not take into consideration latency effects; and (3) they neglect windows of vulnerability in the development of an organism.

Extrapolating from high to low doses takes for granted a single mechanism and neglects a second or third mechanism that may not express abnormalities in the organisms for years after exposure (fetal to adult latency). Because of the mechanism of EDCs and receptors, and the notion of receptor occupancy,
nonlinearities in effects are quite plausible. When all receptors are occupied, additional doses of the endocrine disruptor will not induce a hormonal effect; it can only induce secondary effects not mediated by the estrogen receptor. The new generation of endocrine toxicologists has learned that the saturation of response can occur before the saturation of receptor occupancy (see Figure 11.2).

Another complexity of the endocrine system is that the EDC-receptor ligand may activate different genes, wherein “the activation of different genes requires different numbers of receptors to be occupied” (Welshons et al. 2003: 998). Those studying endocrine disruptors have identified at least two levels in toxicological studies. Level 1 involves high doses and acute toxicity (cytotoxicity or cell death) and does not depend on receptors for the dose response. Level 2 involves low-dose activation of hormone receptors. The dose range of Level 1 is up to 100 million times greater than the dose range of Level 2 (see Figure 11.3).

In 2000, the National Toxicology Program of the National Institute of Environmental Health Sciences (NIEHS) conducted a peer review to evaluate the scientific evidence for reported low-dose effects and dose response relationships for endocrine-disrupting chemicals in mammalian species. Thirty-six scientists made up the subcommittee for the review. They used the following operational definition for low-dose effects: “Low-dose effects were considered to be occurring when a non-monotonic dose response resulted in significant effects below the presumed NOEL expected by the traditional testing programs” (Melnick et al. 2002: 429). The subpanel concluded that “there is credible evidence that low doses of BPA (bisphenol A) can cause effects on specific endpoints” (Melnick et al. 2002: 428). The subpanel also noted that “it is not persuaded that a low-dose effect of BPA has been conclusively established as a general or reproducible finding” (Melnick et al. 2002: 429). The workshop participants drew up a formidable research agenda to narrow the uncertainties about low-dose effects of BPA. One of these proposals could keep a number of research teams occupied for generations, namely, to fully elaborate the mechanism at the molecular level of low-dose interactions.

The American Plastic Council has opposed studies on the reproductive and developmental effects of chemicals claiming that the low-dose effects of BPA

![Figure 11.2. Causal Chain of Endocrine Receptor Mediated Effects.](image-url)
have not been demonstrated. The Council funded a study by a group of scientists in 2003 who applied a “weight of evidence” evaluation of BPA, which included studies published through 2002 on the potential reproductive and developmental toxicity of BPA. The published report stated: “The panel found no consistent affirmative evidence of low-dose BPA effects for any endpoint. Inconsistent responses across rodent species and strains made generalizability of low-dose BPA effects questionable” (Gray et al. 2004: 875). Witorsch (2002) argues that the physiology of the gestation of the mouse differs markedly from that of a human, and therefore low-dose results on mice of endocrine disruptors cannot tell us anything about humans.

Reproducibility of Low-Dose Experiments

Low-dose experiments can be difficult to replicate. Epidemiologic experiments are typically opportunistic and are sometimes carried out when a major chemical spill occurs. Some of the animal studies involve tens of thousands of animals and are almost never replicated because of expense. One of the largest reported tumor studies in a rodent model used 24,000 animals. In a study of the carcinogenic effects of dibenzopyrene (DBP) 42,000 trout were used. The trout were fed as little as 0.45 ppm doses of DBP for four weeks to detect one additional cancer in 1,000 trout (Williams et al. 2003). Even with experiments that involve a small number of animals, replication can be confounded because the strains of the animals are different, the feed is not uniform, or the ambient environment varies between the experiments.

A peer review report from an NIEHS panel wrote: “The major problem with regard to the issue of low-dose effects of BPA and related compounds pertains to the consistency of results from study to study.” The subpanel con-
cluded: “There is credible evidence that low doses of BPA (bisphenol A) can cause effects on specific endpoints. However, due to the inability of other credible studies in several different laboratories to observe low dose effects of BPA and the consistency of those negative studies, the subpanel is not persuaded that a low dose effect of BPA has been conclusively established as a general and reproducible finding.”

A group of scientists published a letter in *Toxicological Science* in response to a previously published research article (Ryan et al. 2010) where rats were fed BPA during pregnancy and lactation and showed no effects on either the male or female offspring. These effects were found in other experiments where the same doses were administered. The authors noted that Ryan et al. used a strain of rats that were quite insensitive to ethinyl estradiol (EE) and therefore they should have used a positive control. They noted: “It is unacceptable in any research with experimental animals to not include both a negative control and an appropriate positive control.” Even when the same strain of mice is used and efforts to repeat an experiment are made, the outcomes may be different. One of the first studies linking BPA to prostate enlargement was performed by vom Saal et al. in 1998.

Two separate studies from other laboratories were conducted in an effort to replicate low-dose effects of BPA using the same strain of mice and following the same research design as the 1998 study. Neither of the follow-up studies showed effects on prostatic weights or daily sperm production. Responding to the failure of replication of their results, vom Saal reported: “A critical issue in experiments concerning effects of low doses of estrogenic chemicals is that a common rodent feed used in toxicological studies has been reported by investigators at the National Institute of Environmental Health Sciences (Thigpen et al. 2003) to be highly variable in estrogenic activity … raising the possibility that endocrine-disrupting components in this feed played a role in the failure of these studies to show low-dose effects of BPA” (vom Saal and Hughes 2005: 929).

John Ashby (2001) wrote in *Toxicology Letters* that different strains of mice yield different effects of BPA. He said that this explains why he was unable to confirm the mouse prostate effects of BPA reported by Nagel et al. (1997). Richard Sharpe of Edinburgh University showed that rats exposed in the womb to octylphenol and butylbenzyl phthalate experienced reductions in testicular weight (Sharpe et al. 1995). The results could not be replicated when Sharpe repeated the phthalate experiment and others repeated the octylphenol experiment (Sharpe et al. 1998).

Vom Saal and Hughes reported a biasing effect of industry-funded papers published on BPA: “As of the end of 2004, we are aware of 21 studies that report no harm in response to low doses of BPA. Source of funding is highly correlated with positive or negative findings in published studies, 94 of 104 (90
percent) report significant effects at doses of BPA, 50 mg/kg/day. No industry-funded studies (0 of 11, or 0 percent) report significant effects at these same doses” (vom Saal and Hughes 2005: 928).

Vom Saal spoke about how companies were interested in striking a deal. After his early BPA prostate studies, he reported: “Dow chemical sent a guy down here and he said we can arrive at a mutually beneficial outcome, where you don’t publish this work on bisphenol A until the chemical industry has replicated your study, and approval for publication was received by all the plastic manufacturers” (Krimsky 2000).

The “funding effect” in science means that the source of funding affects the outcome of a study. The “funding effect” has been demonstrated in a number of studies in biomedical science (Krimsky 2003). It has also been cited in toxicology (Michaels 2008), public health (McGarity and Wagner 2008), global warming (Gelbspan 1997), nutrition (Nestle 2001; Levine et al. 2003) and almost any academic discipline with strong commercial ties. Because of the sensitivity of low-dose experiments, the “funding effect” can be a determining factor in whether low-dose effects become recognized within the scientific community.

Conclusion: Mechanistic Reductionism and Its Role in Policy Stasis

Discussion within the scientific community about low-dose exposures has not changed much in fifty years. It is all about obtaining better data, discovering the biochemical and now genetic mechanisms of foreign chemicals on the human physiology, identifying the uncertainties and proposing a new experiment that will be analyzed, reanalyzed, and meta-analyzed. Ironically, as toxicological science progresses, the uncertainties over the health effects of low doses are not narrowed but broadened because each new experiment raises new questions. The relevant metaphor is the “peeling onion” where for each discovery we reach new depths of uncertainty. It is somewhat paradoxical that more science results in more uncertainty. What we have is a scientific Ponzi scheme, where each payoff (testing a hypothesis) results in new questions, and the payoff, if it ever comes, awaits new experiments that lead to new questions involving new uncertainties.

If the goal of regulatory agencies is to seek closure on the uncertainties before they can regulate a substance, they will forever be grasping for straws. Ana Soto once remarked: “If you are going to study in detail for each chemical, its absorption, degradation and storage, we will never end up with an answer, not in fifty years … no one can tell you for sure about the risks until we run all the experiments … even if we had all this knowledge about the fate of individual chemicals, this might still not be enough” (Cadbury 1997: 180).
If mechanistic reductionism is not the answer to addressing the health and environmental effects of low-dose exposures of chemicals and radiation, then what is? One approach has been comparative risk assessment. If you know that a person receives 100 units of natural radiation a year and a technological device exposes one to the same modality of radiation (ionizing or non-ionizing at the same frequencies) at 0.01 units per year, it can be reasonably argued that the added radiation, ceteris paribus, will not be significant. Current debates in mammography, cell phones, and whole body scans in airports are about the added risks of cancer to incremental exposures or continuous exposures impacting large populations.

There has been a change in perspective and scientific breakthroughs regarding low-level exposure of endocrine-modulating chemicals. Because the endocrine system can be affected by very low doses of hormones, especially during specific windows of embryogenesis, scientists have been able to obtain results using small numbers of animals and thus have not had to depend on linear extrapolations from high doses or large animal populations. While these studies have challenged the assumption that low-dose effects of chemicals are beyond direct human observation, they have had little immediate effect on regulation of the chemicals because industrial lobbyists ask for mechanistic results, replicated studies, and consistency in every experimental outcome. And when we add to the demands the study of combinatorial effects of chemicals, the complexity rises exponentially. Carpy et al. (2000) note: “Despite a large body of knowledge in the field of risk assessment methodologies for exposure to chemical pesticide mixtures, there is no single methodological approach in ‘combination toxicology’ and health risk assessment of chemical mixtures, and therefore professional judgment is still required.”

Alternatives to low-dose toxicology that are not rooted in mechanistic and reductionist models are based on a set of principles that seek to minimize regret and engage the “precautionary principle.” They produce a different set of narratives. Some examples of basic verifiable knowledge claims of potential risk and possible approaches to be taken in response are: (1) chemicals that bioaccumulate in the body; (2) synthetic chemicals that attach to hormone receptors; (3) synthetic chemicals that leach into food in quantities that are hazardous to test animals; (4) synthetic chemicals that interact with important human biochemical pathways; and (5) synthetic chemicals that cross the placenta and expose the fetus.

Suppose we know that some synthetic chemical V found in our food in low doses bioaccumulates in the human body. That is, the human body does not have the enzymes necessary to metabolize the chemical; instead the chemical accumulates in our fat tissue. A reasonable person might ask: Why would I want a synthetic chemical of no known contribution to my health or nutrition to bioaccumulate? Why would I want to be a waste receptacle for a chemical
that is not necessary for my health and well being? Do we need to know the exact mechanism of action of the chemical on my organs or on my genes? Do we need scores of animal tests to determine what the chemical does at high doses and then to extrapolate that to doses that are most common in human tissue? Do we need a series of reproducible tests on multiple endpoints in animals that are proven to model human physiology before a regulatory decision can be made?

In another example, suppose chemical W attaches to hormone receptors in human cells and either blocks or activates the hormone receptor. Do we want to play Russian roulette with our bodies by permitting our exposure to chemicals that bind to our cellular hormone receptors? The xenobiotic hormones mimic the body’s own hormones and may either block or activate genetic mechanisms for hormone production. Unless we have chosen to introduce the xenobiotics for medical therapy, it is reasonable to assume that the chemicals are not likely to benefit the individual and may create harm. A reasonable person would not want to expose themselves to synthetic organic xenobiotics that could be biologically active in unpredictable ways. Once again, do we need to work out all the details of the biochemical pathways with evidence of their pathology to bodily organs or cells before we take prudent steps of precaution? For certain chemicals the effects at high doses may not be the same as the effects at low doses. Extrapolation from high to low doses in these situations will not yield reliable outcomes. Low doses must be studied sui generis despite the difficulty of acquiring reliable data. By virtue of their sensitivity, low-dose experiments are less likely to deliver unambiguous results. Consequently, as a public health precautionary measure, we should find surrogate models of decision making that will not impose imponderable burdens of evidence for demonstrating a risk.

In a third case synthetic chemical X is found in low quantities in fresh and prepared food. Animal studies indicate that the quantities of the chemicals in the food when fed to animals exhibit pathologies. Taking account of safety factors in animal to human extrapolation, is this sufficient to establish a precautionary response to the allowable concentrations of the chemical X in the food supply?

For the fourth case let us assume there is strong evidence in animal studies that a synthetic chemical Y or one of its metabolites interferes with an important biochemical pathway, which is also found in humans. Do we need to demonstrate the effect in human subjects before we take precautionary approaches in limiting human exposure? One such example was discussed by scientists at the University of Lausanne, Federal Polytechnic School and the National Cancer Institute. They described a pathway that involves the pollutant diethylhexyl phthalate (DEHP) and concluded that “exposure to the environmental pollutant DEHP has far reaching metabolic consequences” (Feige et al. 2010: 240).
Finally, in the fifth case, chemical Z is found to transfer from a pregnant mother to her developing fetus across the placenta. Moreover, small quantities of chemical Z are known to have an adverse effect on fetal development. One such case is the transfer of thyroxine (T4) from maternal blood to the embryo. If a xenobiotic chemical Z increases maternal thyroxine (T4), then some of that thyroxine will enter the fetus. With no more information than the importance of a proper balance of T4 to healthy fetal development, that may be sufficient to prevent pregnant women from being exposed to chemical Z (Contempré et al. 1993).

The take-home message of these cases is that the grounds for substituting, banning, or regulating a chemical need not await a complete reductionist analysis of its biochemical and genetic pathways that demand reproducibility and validated animal models that predict human effects. Instead it may be reasonable to act on some commonsense principles that provide precautionary early warning signals.

Notes

1. See, for example, the study by Hunter et al. (1997) published in the New England Journal of Medicine, which some observers believed put an end to speculations that DDT and PCBs could be a cause of breast cancer.
3. Katherine Noyes, “Cell Phone Radiation May Thwart Alzheimers,” TechNewsWorld, 7 January 2010. http://www.technewsworld.com/story/69052.html. “After years of controversy over whether cell phone radiation might cause cancer, scientists have reached the startling conclusion that it might actually cure Alzheimer’s disease. Young mice exposed to long-term radiation equivalent to human cell phone use of a couple of hours a day were protected from Alzheimer’s, and memory function was restored in old mice already afflicted.”
6. Ibid. iv.

Bibliography


Size of Reproductive Organs, Daily Sperm Production, and Behavior.” Toxicology and Industrial Health 14: 239–60.


