



Life in a Contaminated World

Louis J. Guillette Jr. and Taisen Iguchi

Science **337**, 1614 (2012);

DOI: 10.1126/science.1226985

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the targets of newer insecticides, Perry *et al.* have used mutagenesis of *Drosophila* to create strains resistant to spinosad or neonicotinoids; they pinpointed the acetylcholine receptor subunits that are most sensitive to these toxins (17).

The goal of reducing the use of chemical insecticides has spurred the search for biologically based alternatives, a strategy encouraged by Carson [chapter 17 in (1)]. Insecticidal protein toxins from the bacterium *Bacillus thuringiensis* (Bt) are now expressed in more than 58 million hectares of transgenic cotton and maize worldwide to deter lepidopteran pests (18). When Bt cotton was first introduced in the United States and Australia, government-mandated, industry-implemented resistance management plans were in place. These “high dose/refuge” strategies aimed to slow the process of natural selection, first by ensuring that transgenic plants expressed enough toxin to kill all but the most resistant insects, and second by providing non-Bt crops as “susceptibility refuges” on which Bt-susceptible pests could develop to adulthood and mate with the relatively few survivors from the Bt crop. These strategies to delay resistance are working so far in most cases (19).

What if they fail? Estimation of the frequency of rare Bt resistance alleles before they become common enough to cause unsustainable crop damage can provide

advance warning of developing resistance. Using methods based on the inbreeding of large field samples, Downes and Mahon have detected alleles for resistance to the Cry2Ab toxin at frequencies of 0.5 to 0.9% in two species of bollworms in Australia (20). When the resistance gene is known, DNA sequencing can also be used; Zhang *et al.* have correlated mutations in a 12-cadherin-domain protein with bollworm resistance to the Cry1Ac toxin in China (21). Modified Bt toxins have been engineered to circumvent this type of resistance and show promise on other Bt resistance mechanisms as well (22).

Coexpression of an additional toxin, Vip3A, with a different mode of action has been commercialized to delay pest resistance to transgenic crops; however, the Vip3A-resistant allele frequency is already 2.7% in one pest, which is very high given that there has been no prior exposure to this toxin (23).

Forewarned by the long history of insecticide resistance, the deployment of transgenic crops for insect control has incorporated resistance management plans from the beginning. Unfortunately, this has not been the case for transgenic crops engineered for herbicide tolerance. Greatly increased spraying to control weeds in these new crops has led to a rapid rise of herbicide resistance in several weed species (24), and agronomists must now follow entomologists in learning the hard lessons of the past 50 years.

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Acknowledgments: Supported by the Max-Planck Gesellschaft.

10.1126/science.1226994

ECOLOGY

Life in a Contaminated World

Louis J. Guillette Jr.¹ and Taisen Iguchi²

Until the early 1960s, pesticide use was perceived as a benefit to agriculture and public health, with few detrimental consequences. This perception changed dramatically with the publication 50 years ago of Rachel Carson's *Silent Spring* (1). The book was the start of a debate that continues to this day on the relative benefits and risks of not just pesticides but all synthetic chemicals.

Pesticides are unquestionably beneficial for food production (2), but there is a growing awareness of the risks to human and ecological health associated with their use. Over the past decade, a growing literature (3–6)

has examined how early-life exposure to an array of chemical agents, found not only in pesticides but also in personal care products and plastics, can affect human health. The effects on endocrine signaling (and thus endocrine disruption) have been observed in the exposed generation and also in succeeding generations, but the conclusions are not without controversy.

“It is ironic to think that man might determine his own future by something so seemingly trivial as the choice of an insect spray” wrote Carson in 1962 [p. 8 in (1)]. Although she had no mechanism to explain her observations, it is now well documented that exposure early in embryonic development to commonly used chemicals alters gene expression patterns that can lead to altered health later in life (7).

Exposure to pesticides and other chemicals can have complex long-term health effects.

But what dose is required to cause an effect? A large literature in the fields of endocrinology and general physiology demonstrates not only that different effects can be induced at different doses but also that the mechanisms driving those effects can differ as well (7). A report from the Endocrine Society states that different effects should be expected when comparing high- and low-dose regimens of endocrine disruptors (3). Studies using acute high-dose exposures may thus be of limited value for predicting what might occur following the chronic low-dose exposures that almost every population on Earth is subjected to today, often at low but detectable concentrations.

Early-life exposure to chemicals with endocrine disruption potential has been shown to alter gene expression profiles that

¹Department of Obstetrics and Gynecology, Medical University of South Carolina and Hollings Marine Laboratory, 221 Fort Johnson Road, Charleston, SC 29412, USA. ²Okazaki Institute for Integrative Bioscience, National Institute for Basic Biology, Okazaki 444-8787, Japan. E-mail: guillett@muscc.edu

are linked to altered morphology and physiology, such as compromised fertility and reproductive tract development, altered metabolism, obesity, and altered behavior (8–11). The multigenerational relationship between chemical exposure and health has been observed in laboratory models and wildlife (4). Given the heritable nature of some epigenetic modifications (termed germ line–dependent epigenetic modification) (12), the results indicate that the classic “gene by environment” paradigm used to understand environmental impacts on health is incomplete: The parental genome is based on both the genome inherited from the parents (which includes accumulated gene mutations) and the epigenetic modifications that occurred to that genome before fertilization of the new offspring (see the figure).

Much has been made of the inability of some research groups to replicate the endocrine disruptive effects of some chemicals reported by other laboratories (13–15). For example, Hayes *et al.* (16) reported effects on the development of frogs after exposure to environmentally relevant concentrations

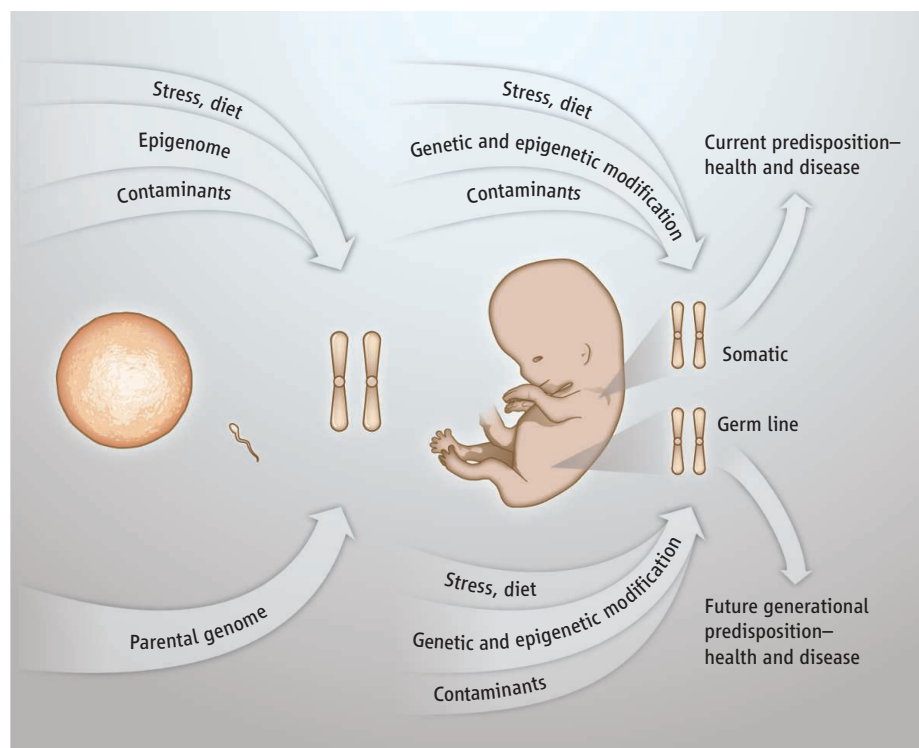
of atrazine, but other groups were unable to replicate these findings (15, 17). However, differences in the design of these experiments did exist, including the source of the animals used and the density at which they were housed (18). Disparate outcomes have also been reported in studies of bisphenol A in rodents that used different designs or methodologies (19) and in studies of human semen quality or genital development (20).

Blount *et al.* have found that in men, perchlorate (a contaminant that affects thyroid function) showed no relationship with the concentrations of thyroid biomarkers. In contrast, in women, raised urinary iodine levels were associated with an influence of perchlorate on thyroid biomarker concentrations (21). Thus, dietary iodine, a key factor influencing urinary iodine output, influenced whether an effect was observed or not. How many studies examining potential effects of contaminants on thyroid function record the iodine concentration in the diet of their research animals?

Other studies also illustrate the complexity of the response to environmental endo-

crine disruptors. For example, Spearow and colleagues have shown in a series of studies that differing strains of mice respond dramatically differently when exposed to the same estrogenic drugs or doses (22). Further, a physical factor such as hypoxia can down-regulate the mixed-function oxygenase enzyme (CYP1A) that metabolizes polycyclic aromatic hydrocarbons and polychlorinated biphenyls, thereby affecting the biotransformation of environmental contaminants, thus altering persistence or even the metabolites present (23). These complex genetic and environmental effects must be taken into account in studies assessing the health effects of environmental pollutants.

Rachel Carson was right: Chemical contaminants play an important role in our health and the health of the environment. We must continue her legacy and focus on how exposure to environmental contaminants, stress, and diet interacts with the human germline genome and epigenome to establish predispositions for disease that are influenced by secondary exposures later in life (5). Understanding this complexity is essential to our understanding of the multiple roles of the environment in promoting those factors that lead to health.



The role of the environment. Environmental factors, including numerous contaminants, have been shown to modify the parental genome, so that the genetic makeup of any offspring is a combination of a parental inherited genome (itself likely influenced by epigenetic mechanisms of the germ line) and environmental influences on that germ line during maturation. Environmental factors such as diet, stress, and contaminants can also modify the genome of the developing embryo by classic selection and mutation or by epigenetic mechanisms at both the somatic and germline levels. These modifications can produce predispositions for health and disease in the current lifetime of the individual. Future transgenerational effects could also be established through modifications in the germline genome or epigenome after exposures during the lifetime of that individual.

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