From *Silent Spring* to Scientific Revolution

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Four decades ago in Silent Spring, Rachel Carson (1962) wove together a fabric of evidence suggesting that parts of the modern chemical revolution were having unintended consequences, undermining human and wildlife health in unexpected ways. At the time that fabric was more Chantilly lace than Afghan rug, with the scientific pattern defined as much by the holes as by the threads of connecting evidence.

Her thesis was compelling, nonetheless. It launched the modern environmental movement. It stimulated a new branch of government focused on environmental impacts. It led to bans of DDT and, since then, a host of other chemicals. Most recently it spurred in 2001 a global treaty, the Stockholm Convention, that requires phase-out and elimination of twelve persistent organic pollutants. And it forced new scientific questions to be asked about links between contamination and health.

Now four decades later, we are midstream in the scientific revolution that her work helped foment. The revolution arises from scientific discoveries which establish that many chemicals --both from the natural world and synthesized in laboratories -- interfere with the biochemical messaging systems that direct the biological development of plants and animals, including humans (Cheek *et al*. 1999; McLachlan 2001).

Virtually all biological development is under the control of various biochemical messaging systems that are involved in the chain of events leading to gene activation and expression. Hormones and growth factors, among others, are key elements of these message systems. Normal healthy development depends on the successful initiation of genetic instructions by hormones and growth factors, among others, which are key elements in these message systems. Disruption can cause immediate effects, ranging from conspicuous teratological impacts to subtle functional disabilities that may not be evident until decades after exposure.

Research now demonstrates that a wide array of chemicals can disrupt these messages without damaging the genes themselves. Much attention has focused on disruption of hormonal signaling, which has become known as endocrine disruption (Colborn *et al*. 1996).

Investigation of developmental disruption has burgeoned during the past decade because of research funding by European, Japanese and North American governments. New results are published virtually every week in journals like Environmental Health Perspectives, Human Reproduction, Toxicology, and Environmental Science and Technology.

For example, a study published in September 2002 by a research group in the Netherlands documented associations between variations in background levels of in utero exposure to certain organochlorine chemicals and gender-specific play behavior in children (Vreugdenhil *et al*. 2002). Boys with relatively higher levels of PCB exposure were less likely to engage in play behaviors typical for boys; girls more likely to engage in play behavior typical for boys. Boys with relatively higher levels of dioxin were more likely to engage in more feminine play behaviors, as were girls.

These findings are especially noteworthy because the levels of exposure were not that high, but instead represented variations around background levels common in European women. Moreover, these outcomes are consistent with experiments carried out with laboratory animals examining exposure impacts on sex-specific behaviors.

The same research group had recently published studies demonstrating impacts of in utero exposure on cognitive development and immune system function (Huisman *et al*. 1996, Koopman-Esseboom *et al*. 1996, Weisglas-Kuperus et al. 2000). Their groundbreaking studies rest on detailed tracking of the development of a cohort of individuals beginning with measurements of the mothers' serum contamination during pregnancy, with careful attention paid to potential confounding variables.

New results like these are legion (Myers 2002). They are forcing a series of conceptual shifts upon toxicology as it integrates these new findings with long-standing assumptions. These shifts are summarized in Table 1. The text below examines several in greater detail.

Table 1. Conceptual shifts

Old	New
High level contamination overwhelms detoxification and other defense mechanisms	Low level contamination hijacks control of development
"The dose makes the poison"	"Non-monotonic" dose response curves are common, in which low level exposures cause effects that disappear at higher levels
Only high levels of exposure matter	Impacts caused at what had been assumed to be "background" levels
Focus on adults	Periods of rapid growth and development (prenatal through puberty) are most sensitive to exposure
A small number of "bad actors"	Many chemicals thought safe are biological active and capable of interfering with signaling systems
Immediate cause and effect	Long latencies are common; fetal programming can lead to disease and disabilities decades later
Examine chemicals one compound at a time	In real life, mixtures are the rule. They can lead to effects at much lower levels than indicated by simple experiments with single chemicals.
Focus on traditional toxicological endpoints like	Wide range of health endpoints, including

mutagenesis carcinogenesis, cell death	immune system dysfunction (both hyper and hypo-active); neurological, cognitive and behavioral effects; reproductive dysfunctions; chronic diseases
One-to-one mapping of contaminant to disease or disability	Same contaminant can cause many different effects, depending upon when exposure occurs during development and what signals it disrupts. Multiple contaminants can cause same endpoint, if they disrupt the same developmental process.

Traditional toxicology focuses on damage, such as cell death, mutations or genotoxicity that occurs typically when cellular biochemical defense mechanisms are overwhelmed. At high exposure levels many chemicals implicated in message disruption are toxic in these traditional ways. At lower levels of exposure, however, their impacts instead involve, in essence, hijacking control of development, adding or subtracting to the body's own control signals at remarkably low levels of exposure. A vivid recent example is the discovery that a widely used herbicide, atrazine, causes tadpoles to develop into hermaphroditic adults at a level of exposure approximately 30,000 times lower than traditional toxicological work had identified as toxic to frogs (Hayes *et al*. 2002). The mechanism appears to involve enhancement of aromatase conversion of testosterone to estrogen during development. Elegant theoretical and empirical work suggests that for activated signaling systems, there may be no threshold beneath which no effect occurs (Sheehan *et al*. 1999).

Another key shift is the acknowledgement that the assumption that "the dose makes the poison" can be misleadingly simplistic, if it is used to imply that only high dose exposures induce effects. In fact, low exposure levels sometimes cause effects not seen at higher levels (e.g., vom Saal *et al*. 1997, National Toxicology Program 2001, Cavieres *et al*. 2002). Researchers are now intensely pursuing these "non-monotonic dose response curves" and the uncertainty about their underlying mechanisms, which likely vary from case to case. One plausible hypothesis is that at low, "physiological" levels, the contaminant interferes with developmental signaling but does not activate biochemical defenses against impacts that would be caused by higher exposures. At somewhat higher levels, these defenses are activated and the contaminant is successfully detoxified. At even higher levels, the defense mechanisms are overwhelmed by the toxicant and more traditional toxicological effects are induced.

As scientific research has focused on mechanisms of message disruption, it has implicated a wide array of chemicals. This expansion has involved both ongoing identification of compounds capable of interfering with estrogen, which was the initial focus, as well as research broadening the range of message systems studied. Some of the most troubling discoveries about "new actors" is that they involve compounds in widespread use in consumer products, including plastic additives like

phthalates and plastic monomers like bisphenol A, which leaches from polycarbonate products (e.g., Gray *et al*. 2000, Masuno *et al*. 2002).

That is not to say that we have complete understanding of even the best known contaminants. This reality was highlighted by a study published in 2001 about DDT, in which Longnecker *et al*. (2001) report a highly significant association between DDT in maternal serum and the likelihood of preterm birth. Their study used birth records and stored serum from the mid 1950's – '60s. They concluded that the US had experienced a hitherto undetected epidemic of preterm birth during this period because of DDT use. Longnecker (pers. comm.) went further to estimate that because of the close association between preterm birth and infant mortality, up to 15% of infant mortality during that period may have been attributable to DDT use.

Disrupting chemicals have been identified that interfere with estrogen, androgen, progesterone, thyroid, insulin and glucocorticoid signaling, among others. The mechanism does not always involve mimicking (or inhibiting) ligand-receptor binding. For example, as noted above, atrazine appears to enhance aromatase conversion of testosterone to estrogen.

Signal disruption may also intercede in steps leading to gene activation after ligand-receptor binding. This was established by in vitro experiments showing that arsenic selectively inhibits gene activation by the glucocorticoid- receptor complex after normal ligand-receptor binding and subsequent entry into the cell nucleus, at arsenic concentrations far beneath cytotoxic levels (Kaltreider *et al*. 2001). While human health impacts have yet to be demonstrated via this mechanism, dysfunctions in glucocorticoid action have been linked to weight gain/loss, protein wasting, immunosuppression, insulin resistance, osteoporosis, growth retardation, and hypertension.

Another important issue raised by emerging science is the powerful interactions that can occur within mixtures of chemicals, even though regulatory toxicology is conducted virtually exclusively on pure single compounds. Two results published in 2002 emphasize the importance of considering mixtures: In the first, Rajapakse *et al*. (2002) demonstrated that a mixture of estrogenic compounds, each present at a level beneath that capable of producing a statistically detectable estrogenic response in an in vitro system, combined to more than double the response of the system to 17ß-estradiol. In the second, Cavieres *et al*. (2002) found that a common off-the-shelf dandelion herbicide mixture strongly reduced fetal implantation rates in mice at one-seventh the concentration considered safe for its principal herbicidal component, 2,4-D, by the US Environmental Protection Agency.

The issue of mixtures is complicated further by interactions now known to occur between contaminants and infectious agents. Large increases in disease risk can be associated with simultaneous exposure to contaminants and infectious agents. For example, Rothman *et al*. (1997) reported a >20-fold increase in relative risk to non-Hodgkins Lymphoma with combined exposure to elevated (but still background) PCBs and Epstein-Barr virus. The mechanism underlying this result is

unknown, but is possibly due to well-established immune system impairment by PCBs. If this mechanism is widespread, then current estimates of morbidity and mortality due to contamination are likely to be unrealistically low. Immune system interference by a variety of contaminants is widely reported (e.g., Baccarelli *et al.* 2002).

Together these conceptual shifts are also challenging the adequacy of current epidemiology to guide regulatory standards. The patterns underlying these conceptual shifts—including (i) non-monotonic dose response curves; (ii) windows of vulnerability during development; (iii) the ubiquity of mixtures; (iv) the likelihood that multiple chemicals can induce similar impacts via disruption of developmental processes; (v) the same chemical can cause different impacts depending upon when exposure occurs; (vi) long latencies between exposure and manifestation of impact in a mobile population, etc.—all increase the likelihood of false negatives in epidemiology as it is currently practiced.

Thus the revolution in science that Rachel Carson stimulated raises today a series of troubling questions about whether current health standards truly protect public health. Effects of low level, background exposures are likely to be far more widespread than acknowledged, and involve many more health endpoints than traditionally considered, yet these new mechanisms of toxicity thwart the epidemiological tools now available to establish human harm.

We are confronting an enormous gap between what science now tells us about the links between contamination and health, and the antiquated approaches still used to safeguard public health. Health professionals will be important contributors to narrowing that gap, first by informing themselves about the underlying science, and then by helping to advance public understanding of the emerging evidence. Carson's scientific revolution can drive a transformation in public health that reinvigorates investments in prevention through exposure reduction.

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