21st Century Toxicology and its Implications for FDA Regulation of Food-Contact Substances

by Jane Muncke and Stephen Paul Mahinka

Groundbreaking scientific ideas have a history of initial refusal: think of Galileo Galilei and his paradigm-shifting concept that the sun, not the earth, is at the center of our planetary system. He certainly was not popular at the time with some, but we all know that in hindsight many of his ideas were proven scientifically correct. There are many other similar examples throughout the history of science—with good reason.

Science is about describing our world with the help of models. These models are as such best available descriptions of observations, or measurements. Measurements always depend on the available technology. Galileo's innovative experimental approach lead to the new, solar centric, model, and it was enabled by a new telescope he constructed himself. So when thinking about good science, the question to ask is: If new observations do not fit the existing model, do we discard the observations as faulty, or do we improve our model? So too with regulatory science: if new scientific approaches do not fit the traditional Food and Drug Administration (FDA) model of assessment of food contact substances, does FDA disregard the new analyses or alter its assessment approach?[1]

A paradigm shift is happening in the toxicological sciences today, and their relation to assessment of food-contact substances.[2] Toxicology largely has been based on Paracelsus' threshold principle, with its aphorism: "solely the dose determines that a thing is not a poison."[3] Paracelsus, who died some decades before Galileo was born in the 16th century, had quite different measurement tools compared to today's life sciences researchers. It should therefore not come as a surprise that technological innovations in scientific instruments came hand in hand with new observations, and these begged for creation of new descriptive models.

One such new scientific observation is the so-called "low dose" effect.[4] Today, there is an increasing body of scientific literature documenting observations of low dose effects in biological systems (animals and cell lines).[5] These studies often imply innovative measurement methods, enabled by 21st Century technology. Many of these studies have been independently replicated and confirmed.

The underlying model for low dose observations (apart from carcinogenic compounds) is that certain chemicals can interfere with the body's hormone system. Hormones are signaling molecules that enable communication between different organs and cells; they move with our blood through our bodies and trigger development, growth, metabolism, brain function, immune system effects, reproduction and so forth.

The pivotal role of signaling chemicals was fully recognized around 15 years ago when scientists showed cross-talk between the endocrine, immune and nervous systems.[6] These systems were previously believed to be distinct from one another, and this scientific finding led to a new scientific model, today undisputed, describing the mind-body link.

Hormones are thus critical for maintaining health. Some chemicals can disrupt normal hormone function.

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Consequently they have been termed hormone disrupting chemicals, or endocrine disrupters. Their effects range from mimicking natural hormones by binding to the hormone receptors, blocking receptors for natural hormones, to interference with gene expression, blocking of hormone-producing enzymes, occupation of hormone blood transport protein and many other effects.

The poster child of hormone disrupters currently is bisphenol A. Today, there are more than 1700 toxicological studies published on this compound.[7] These studies often use modern methods of toxicogenomics[8] and show that bisphenol A is a potent chemical that is biologically active. It mimics the natural female sex hormone estrogen in some cases, in others it blocks estrogen or has different effects all together. For example, bisphenol A induces insulin in the same way as the same dose of estrogen does. On the other hand, in nerve cells, low doses of bisphenol A block estrogen action. Recently, bisphenol A was found to be far better than estrogen at binding a newly discovered estrogen-related receptor.[9]

What is the relevance of these findings for public health and, consequently, for FDA food additive regulation?

The consequences of such effects are not necessarily adverse. If the body's natural function is constantly disrupted by exogenous hormones, however, disease will develop over time. In the case of insulin, a constant stimulation of production leads to insulin resistance[10]—the starting point for diseases like diabetes type 2.[11] In fact, we are seeing a constant increase in such diseases in the general population (nearly 8 percent of the U.S. population is diabetic,[12] every third American adult is obese).[13] Apart from a surge in healthcare costs, this also implies impaired quality of life. No clear link has been established between bisphenol A exposure in humans and the cause of diabetes type 2, but the available science warrants a dedicated exploration of this hypothesis, by both scientific researchers and FDA regulators.[14]

Today, endocrine-disrupting chemicals generate a substantial potential concern for public health. The Endocrine Society, for example, recently released a Scientific Statement, after reviewing 485 articles, noting as a "key point" that: "The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis."[15]

Another recent paradigm-shifting finding for toxicology is the development of mixture toxicity. Single chemicals have individual thresholds for exerting their effects, as described by Paracelsus. But if there are several chemicals in a mixture that target the same biological endpoint, they can act additively, or even synergistically. This happens even if the single chemical is present in the mixture below the threshold level. Hence, the effect of the mixture can be larger than predicted from the effects of the individual components of the mixture. This mixture toxicity effect was dubbed "something from nothing."[16]

Given the abundance of chemicals in use today (in the European Union (EU) more than 100,000 chemicals are used for industrial purposes,)[17] mixture toxicity is a serious issue, particularly since all people carry undefined mixtures of chemical pollutants in their bodies. The Centers for Disease Control and Prevention (CDC) measure human body burdens of chemicals in U.S. inhabitants. Data for nearly 150 different compounds are currently available from 2001-2002.[18] The CDC findings show broad exposure of people to many different chemicals, with unknown long-term health consequences and suspected links to diseases like breast cancer.[19]

Of greatest concern is the widespread exposure of developing fetuses and children to chemicals. This concern has arisen over the last few decades, starting in the 1960s with the drug thalidomide, a sedative. A single pill, if taken during the first trimester of pregnancy, led (among other effects) to severe malformations of arms and legs in newborns. Most thalidomide victims were recorded in Germany. The U.S. had been spared this tragedy thanks to a careful FDA scientist refusing to agree to marketing approval. Before these tragic incidents, an unborn child was believed to be shielded from chemicals by the placenta. Today we know that the fetus is exposed to body-foreign chemicals just like adults are. Many industrial chemicals have been measured in umbilical cord blood and amniotic fluid.

Exposure of developing fetuses and children to chemicals that disrupt hormone signaling consequently is of high concern to scientists. During development, the scaffolding of life is constructed, the metabolism is programmed, the brain is formed, and all other organs are made. These developmental stages are highly complex and intricately controlled. If certain chemicals can interfere with this normal development, children can be born looking healthy and normal, but they can grow up to develop chronic disease as adults.

This long-term legacy is only being fully understood today, by reason of careful statistical analysis and increasing attention by scientists to this issue.[20]

In 1986, the epidemiologists David Barker and Clive Osmond published a study on risks for ischemic heart disease. Ischemic heart disease can lead to heart

attack and it is the most common cause of death in Western societies.[21] The ruling paradigm at the time was that an increase in prosperity and subsequent affluent lifestyle (meaning higher consumption of red meat, fatty foods, a lack of exercise) would cause the disease.

Barker and Osmond proposed a new hypothesis, based on their study of pre-war birth registries: heart disease starts in the womb. They found a proportionally higher incidence of the disease during 1968-1978 in persons born in less affluent communities and linked this to increased infant mortalities in the same communities during 1921-1925. Death of infants was attributed largely to the lack of food in the poor communities. Malnutrition of the developing fetus in these poorer communities thus was shown to be a major cause of adult heart disease some 50 years later.

At the time, this hypothesis was disregarded. Now, it is widely accepted. It is known as "the Developmental Origins (or Basis) of Adult Disease," and it includes the fetal, neonatal, and childhood development stages. New animal studies are showing that many other chronic diseases and even obesity are caused by disrupted development, where the causes of impaired growth can be manifold, including fetal exposure to hormone disrupters. Important large-scale prospective studies are now systematically investigating these links in humans.[22]

Protecting the developing child from adverse effects, like those caused by harmful chemicals at low doses or in mixtures, increasingly appears to be an important first step in long-term disease prevention. Consequently, at least minimum measures based on this developing science must address children, adolescents (i.e., teenagers during puberty) and women of reproductive age alike.

Finding agreement on what such minimum measures would be is part of the current scientific debate about bisphenol A (BPA). At its core, this debate focuses on the gap between basic research and its proper incorporation within regulatory toxicology. While some government agencies such as the National Institutes of Environmental Health Science (NIEHS) can fund basic research in this area, this science is generally not easily translated to policy making. Regulators thus may turn to industry-funded science—designed for the purpose of risk assessment—to reach decisions. This reliance with respect to re-evaluation of BPA has led to serious questions about whether regulators can completely rely on such studies for risk assessments.[23]

Recently, NIEHS developed a special initiative on the effects of bisphenol A, intended to fill the data gaps for policy decision making. First results from these six to eight larger studies, addressing multiple endpoints and covering a wide dose range will be available in the next few years.[24] Such studies should be of further assistance in informing regulatory science with 21st century toxicology.

In the authors' view, there thus is significant new toxicology evidence of low-dose effects and synergistic effects of endocrine-disrupting chemicals, which FDA properly should seriously consider in evaluating the health effects of such substances in food-contact applications.

1 A recent article by Heckman, J., *Political Toxicology and Its Impact*, FDLI Update 45 (Mar./Apr. 2009), takes such a dismissive approach to this developing new toxicology, arguing for no change in FDA's long-held assessment methodology for food-contact substances. Institute of Food Technologists (IFT) Expert Report, *Making Decisions About the Risks of Chemicals in Foods With Limited Scientific Information*, 8 Comprehensive Reviews in Food Science and Food Safety 269, 272–74 (2009).

2 Myers, J. P., Zoeller, R. & vom Saal, F., *A Clash of Old and New Scientific Concepts in Toxicity, with Important Implications for Public Health*, Environmental Health Perspectives (2009), in press.

3 Often misquoted as *dosis sola facit venenum* (the dose makes the poison). Deichmann, W. B., Henschler, D., Holmsted, B. & Keil, G., *What is there that is not poison? A study of the Third Defense by Paracelsus*, Arch Toxicol (1986), 58, (4), 207-213.

4 *See* Myers, J. P., note 1 *supra*, arguing against the validity of use of high dose testing to predict low dose effects for contaminants that behave like hormones.

5 Here, low dose refers to environmentally relevant levels of chemicals, at levels measured in human serum or urine.

6 Chesnokova, V. & Melmed, S., *Minireview: Neuro-immuno-endocrine modulation of the hypothalamic-pituitary-adrenal (HPA) axis by gp130 signaling molecules*, Endocrinology (2002), 143, (5), 1571-1574.

7 PubMed http://www.ncbi.nlm.nih.gov/sites/entrez.

8 Toxicogenomic tools allow measuring how genes are turned off and on. Normal and diseases states can be compared to identify changes in gene expression, and this can also be applied to learn the mechanism of poisoning by a chemical. Today it is known that changes in a gene's DNA sequence, as well as changes in the way genes are turned off and on, are heritable.

9 In fact, estrogen does not seem to bind this receptor at all.

10 Alonso-Magdalena, P., Morimoto, S., Ripoll, C., Fuentes, E. & Nadal, A., *The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance*, Environ Health Perspect (2006), 114, (1), 106-112.

11 Biddinger, S. B. & Kahn, C. R., *From mice to men: insights into the insulin resistance syndromes*, Annu Rev Physiol (2006), 68, 123-158.

12 http://www.cdc.gov/media/pressrel/2008/r080624.htm.

13 http://www.cdc.gov/nchs/pressroom/07newsreleases/obesity.htm.

14 For a more detailed review of the need for updated assessment of endocrine-disrupting chemicals according to contemporary scientific knowledge, *see* Muncke, J., *Exposure to endocrine disrupting compounds via the food chain: Is packaging a relevant source?*, Sci Total Environ., (2009), 407, (16), 4549–4559.

15 Diamanti-Kandarakis, E., et al., (2009), *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement*, Endocrine Reviews 30 (4): 293-342.

16 Silva, E., Rajapakse, N. & Kortenkamp, A., *Something from 'nothing'—Eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects*, Environmental Science & Technology (2002), 36, (8), 1751-1756.

17 http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=ein

18 http://www.cdc.gov/exposurereport/report.htm.

19 http://www.chemicalshealthmonitor.org/spip.php?rubrique100.

20 http://www.pptox.dk/Consensus/tabid/72/Default.aspx.

21 Barker, D. J. & Osmond, C., *Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales*, Lancet (1986), 1, (8489), 1077-1081.

22 Trasande, L., et al., *Environment and obesity in the National Children's Study*, Environ Health Perspect (2009), 117, (2), 159-166.

23 Myers, J. P., *et al.*, *Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A.* Environ. Health Perspect. 2009, 117, (3), 309-315; Tyl, R.W., *Basic Exploratory Research Versus Guideline-Compliant Studies Used for Hazard Evaluation and Risk Assessment: Bisphenol A as a case study.* Environ. Health Perspect. 2009, in press.

24 Heindel, J., National Institutes of Environmental Health Sciences (NIEHS): Personal Communication to J. Muncke, 2009