As we saw in RACHEL'S #754, the science of toxicology has been fundamentally altered by the discovery, 20 years ago, that some industrial chemicals can interfere with hormones in plants and animals including humans.

For over 450 years the phrase "the dose makes the poison" has been used to justify the dispersal of exotic, biologically active chemicals into the environment because if "the dose makes the poison" then low doses received through air, water and food shouldn't matter. Unfortunately as we have seen, low doses DO matter because:

(a) individuals differ in their inherent (genetic) sensitivity;
(b) we are all exposed routinely to mixtures of individual chemicals, and harmless amounts of individual chemicals can combine to create harmful mixtures;
(c) some chemicals are only biologically active during particular times in the development of an organism, so their toxicity must be assessed during those exact times -- otherwise chemicals may be deemed biologically weak or inert when in fact they are powerfully active.

There are other serious problems with chemical regulations: premised on the idea that "the dose makes the poison." The phrase assumes that the greater the dose the stronger the poison. Because of this assumption, chemicals are routinely tested on laboratory animals in high doses because high doses are assumed to provoke the greatest effect.

We now know that this is not always true and that sometimes the opposite is true. Sometimes low doses produce greater effects than high doses. For example, in RACHEL'S #754, we described a study of Bisphenol A which found that low doses of Bisphenol A produced a greater biological effect than higher doses. (EHP Vol. 109, No. 7 [July 2001], pgs. 675-680.) In other words, the "dose response curve" for Bisphenol A is shaped like an upside-down (or inverted) letter U. Initially, as the dose rises, the response rises. However, at some point as the dose continues to rise the response stops rising, then begins to diminish and falls back toward zero.

It is now well-established that many hormone-disrupting chemicals exhibit this inverted-U dose-response curve. Such chemicals disrupt hormones at low doses but not at high doses. What seems to happen is that the hormone system becomes overwhelmed and stops responding, so at high doses there is no observable effect. This turns Paracelsus on his head.

In addition to the Bisphenol A study mentioned above, two studies published recently in EHP demonstrate an inverted-U dose-response curve. First, phytoestrogens (estrogens in plants, such as soybeans) at low doses inhibit the production of estrogen; at higher doses the inhibitory effect disappears and the phytoestrogens behave like estrogen itself, adding to the effect of the body's own natural estrogen. The dose-response curve is an inverted U. (This may explain why low doses of phytoestrogens protect against breast cancer, the authors say. See EHP Vol. 110, No. 8 [August 2002], pgs. 743-748.)

Second, a study of adult male guppy fish, exposed to certain pesticides in their food (vinclozolin and DDE, which are known to disrupt male sex hormones) exhibited shrunk testes, a significant reduction in numbers of sperm, and "a severe disruption in male courtship behavior." Some of the measured effects were greater at a lower dose, demonstrating an inverted-U dose-response curve. (EHP Vol. 109, No. 10 [October 2001], pgs. 1063-1070.)

The authors of the guppy study did a literature search and found over 100 published papers reporting an inverted-U dose-response curve, so this phenomenon is well-established.

This means that traditional toxicological testing at high doses may miss important effects that only occur at lower doses. Therefore, low doses will have to be tested.

So Paracelsus's phrase should now be, "The dose of the mixture makes the poison, but differently for genetically different individuals and differently at different times during growth and development, always mindful that lower doses may be more poisonous than higher doses."

This modern rendition of Paracelsus makes it clear that adequate toxicity testing is enormously more complex (and therefore much more expensive) than anyone imagined even 10 years ago.

But the difficulties for modern toxicological science do not stop there. After we published RACHEL'S #754, Albert Donnay of MCSI Referral & Resources (adonnay@jhu.edu, and http://www.mcsrr.org/), pointed out that any study of any toxicant or other stressful exposure is worthless unless it accounts for (and controls for) each subject's degree of adaptation to the toxicant, which depends not just on their degree of genetic sensitivity but also on the timing, intensity and pattern of their prior exposure.

Adaptation to toxic stressors, also known as acclimatization, habituation or tolerance, is a general phenomenon in humans and other animals. We are all familiar with adaptation from our experience with smokers. When you inhale your first-ever cigarette, you have an immediate powerful reaction: light-headedness, heart palpitations, perhaps a general feeling of illness including nausea. If you persist in inhaling cigarette smoke, you get used to it, you become "adapted." Pretty soon you notice that you get a certain "lift" from smoking. Then you become so adapted that you have to smoke more and more to get the "lift" you want.

We recognize adaptation in people's everyday experience with cigarettes, alcohol, and pharmaceutical drugs. It also occurs on the job where workers can smell strong chemical odors when they first go to work (for example, in dry cleaning shops) but after a while their sensory awareness of the odors disappears even though the odors are still present and noticeable to others who are not habituated to them. This is adaptation.

Adaptation may occur in response to all kinds of stimuli - - not just chemicals but also noise, light, touch, heat or cold, and altitude. In his medical textbook, THE HUMAN SENSES, Frank A. Geldard writes, "A decline in sensitivity with continuing action of a stimulus is a very general phenomenon in sensory physiophysics and one which intervenes significantly in nearly all experimental situations."[1, pg. 299] Discussing adaptation to taste sensations, he writes, "Taste receptors have their sensitivity automatically reduced by being exposed to a continuous unvarying stimulus, just as olfactory [smell] organs do under analogous conditions. In fact, the addition of the sense of taste completes the catalogue of sense departments displaying adaptation; this has been found to be an entirely universal phenomenon in the world of sensation."[1, pg. 513]

The other side of the coin from "adapted" is de-adapted or "sensitized." When smokers give up cigarettes for a period of time, they find that they have become "sensitized" to second-hand smoke. They now notice and react to much lower levels of exposure than they previously tolerated, moreso even than the average ("naïve") person who has never smoked. Sensitization lies at the other end of the sensory spectrum from adaptation.

So people and laboratory animals vary in their degree of adaptation, depending on their prior exposure. For any given stimulus, including toxic chemicals, the naïve (never-exposed) animal, the adapted...
animal, and the de-adapted or sensitized animal all react differently.

Classic studies of carbon monoxide reveal the importance of "degree of adaptation." Carbon monoxide is an odorless, tasteless, colorless gas created by incomplete combustion of carbon fuels. Your automobile engine and gas cook stove give off carbon monoxide. Carbon monoxide displaces oxygen from your red blood cells and other heme proteins, so a high dose can kill you.

In 1940 Esther M. Killick studied carbon monoxide in detail and reported her findings.[2] Killick reviewed a 1906 study of guinea pigs kept in enclosed cages to which carbon monoxide was introduced in measured quantities. When the carbon monoxide level was slowly raised over a period of several weeks, the guinea pigs could adapt to 45% saturation of carbon monoxide in their blood without apparent ill effect. But when naive animals were introduced abruptly into this same environment, they died within a few days. So studies of the toxicity of carbon monoxide will yield dramatically different results, depending upon the degree of adaptation of the subjects being studied. So it is with other toxicants.

At this point Paracelsus's "dose makes the poison" has become "The dose of the mixture makes the poison, but differently for genetically different individuals and differently at different times during growth and development (always mindful that lower doses may be more poisonous than higher doses), and differently depending upon the subject's prior history of exposure to this mixture and their degree of adaptation (or sensitization) acquired as a result of that history."

By now it must be clear that, in the practical world of everyday science, testing of chemicals for their effects on environment and health should entail studies of naive animals, habituated animals, and sensitized animals. The subjects should be exposed to mixtures of chemicals in addition to individual chemicals and the exposures should occur at crucial times during growth and development. (Discovering those crucial times is a major challenge by itself.) The effects being studied should include not only physical changes in the subject, but also behavioral changes (for example, the guppy's courtship behavior, or a human's ability to concentrate or tendency toward violence). Effects on offspring must also be studied because some exposures leave the exposed parents seemingly unchanged yet damage the second and subsequent generations of offspring. These ideas --not "the dose makes the poison" -- should form the basis of chemical regulations.

In sum, the simple idea that it's OK to put biologically active chemicals into the workplace, into products, or into the environment because "the dose makes the poison" is a dead letter. It is an idea whose time has gone. It is false, misleading, utterly without merit.

The corresponding idea, that if we just study long enough we'll discover, for every chemical, a dose that is "safe" for an entire population of workers, consumers, and the general public, is also false, misleading and dangerous. It is dead wrong, because there are not enough laboratories in the world to carry out the needed investigations on all 80,000 chemicals now in use, nor enough peer-reviewed journals to report the results. There are just too many variables to be taken into account simultaneously. This means that relatively few chemicals will ever be adequately tested.

If we admit to ourselves that our present system of chemical regulation is based on false premises and cannot be fixed, we can begin anew and think in terms of precautionary action: put the burden of demonstrating safety onto the manufacturers of chemicals. Chemicals lacking adequate evidence of safety by a certain deadline will be earmarked for phaseout. This will force corporate managers to choose which chemicals they really believe are worth salvaging, and these will be studied feverishly. The others will eventually be phased out and disappear. The universe of industrial chemicals will shrink to a much smaller number, and those remaining will be much better understood. Such a change will be good for everyone.