Buffalo Environmental Law Journal

Volume 8 | Number 2 Article 4

4-1-2001

Science and Health Risks Research Since Love Canal

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Good afternoon, I'm Jim Olson from the department of Pharmacology and Toxicology at UB. It seems that all of us have some unique perspective to Love Canal and I'll give you mine. In 1978-1979, I was at Vanderbilt University conducting research on dioxin in the Toxicology Center there and was recruited to UB as a junior faculty member during the summer of 1980. As you might have heard from Dr. Naughton, that was when several Love Canal study groups were meeting in Medical school. I was invited to one of these meetings to discuss how the University and the CDC would go about conducting a study of the current state of the health of the people living near Love Canal.

We discussed issues about how we were going to transport blood from the residents back to the University labs to do some testing. I was at perhaps two of these meetings and that was it, once it was clear the study was going nowhere. Unfortunately this large group that seemed to have a clear direction disbanded and no further action was taken. Since that time, a great deal of scientific knowledge has been gained particularly regarding some of the issues that were brought up at the Love Canal. Since I followed John Vena, I really hated to show this first overhead. John may think of epidemiology as the sun, at the center of the universe, and everything revolves around this discipline and all answers can be obtained through epidemiology. But it's not true. In fact, there may be steps along the way, and what I am trying to show on this overhead are some of these steps going from A to J. In the case of the Love Canal, you have a pretty well defined "A"—we have a geographic area with residents. In "B" we really try to look at the issue of exposure to these chemicals. Many dollars were spent to identify what chemicals were present at the Love Canal. We had a pretty good idea of what was in the area. But

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what we have virtually no knowledge on, and still don't with regards to these Love Canal residents, is the absorbed dose. What is really being absorbed into the individuals? What is the human body burden of these chemicals? I will talk about this later. This is a very critical part of any attempt to link an exposure to an outcome or to a disease. That is the problem we had twenty years ago and still have today, linking exposure to a human disease or adverse health outcome.

What I think this figure does is help illustrate the steps along that pathway between exposure and disease, and I will go through some of these step by step. Again, at Love Canal, while we had good information on what was there, we had virtually no information on what chemicals were being taken up by people. Thus, we really didn't know anything about the biologically active dose that was at a critical target site. Obviously if we're looking for genetic effects or cancer it would be important to know what chemicals were associated with DNA; that would be a very critical marker at a critical target site. Again, there was no data on that endpoint. Once the chemical gets to the target site, we can look at the more mechanistic questions of the quantitative association between the chemical reacting with the target and the actual toxicity that might be occurring.

These types of studies in block "F" are things toxicologists typically do with laboratory animal models or cell culture models, where we really look at quantitative associations between the chemical and an adverse affect. Prior to there being a clinical symptom or disease, there are early markers predictive of potential toxicity. These could be biochemical or functional markers, perhaps a change in an enzyme level or perhaps a decrease in a serum protein. They're very much at a subclinical level but very indicative of a potential to elicit an adverse health outcome. Ultimately, these early biomarkers may lead to the eventual clinical disease syndrome, which could be quite extensive by the wide range of chemicals that were present at the Love Canal. Again, epidemiology can really intersect with many of these boxes, and that's where these solid lines come into play. I tried to link monitoring of the dose with biological plausibility. Is there a connection that would really link the dose with an adverse effect, to assist efforts to monitor these effects? That's

where toxicologists, epidemiologists and chemists need to interact in a team approach to address these questions.

A few more toxicological principles require further clarification. I tend to think of exposure as simply the potential to receive an internal dose of a substance. There were exposures at the Love Canal where there was an opportunity to receive an internal dose of a chemical. That was well documented. There was a lot of material sitting there. But whether an internal dose occurred, we really don't know because an internal dose is defined as the amount of substance that is absorbed—the amount present in the cells, tissue, or body fluids. There are some examples of how we might determine an internal dose. In the case of something like high-chlorinated biphenyls (PCBs)—they are very persistent, cumulative chemicals—they don't degrade and are resistance to all forms of degradation. So we have to measure these chemicals typically in serum, breast milk, or adipose tissue. They are very lipophilic . They have a high affinity for fat and that is where you look for them—in fatty tissues.

Let's consider the example of cigarette smoking, which I consider to be a good example of an environmental hazard. Rather than looking at nicotine in the blood as a marker of exposure to cigarette smoke, people typically look at cotinine, which is a metabolite of nicotine. The biological half-life of cotinine is much longer than the biological half-life of nicotine so it tends to be a better or more reliable marker of exposure to cigarette smoke. There are some other markers that can be used when we are estimating a biologically effective dose—or the amount of the chemical interacting with critical target sites. In the case of chemical carcinogens, it is ideal to understand the interactions of the carcinogen directly with DNA or proteins. Organophosphate insecticides are an example of a non-cancer causing chemical, which inhibits the enzyme acetyl cholinesterase. Cholinesterase inhibition is a good marker of exposure and the neurotoxic effect of this class of insecticides.

Over the last twenty years we have also been trying to address the issue of sensitivity or variability between individuals. Susceptibility is an issue that toxicologists and people in public health are trying to deal with in designing clinical studies because

individuals respond to chemicals to a greatly varying degree. Why is there this variability? It could depend on a drug-metabolizing enzymes that vary with the population. It could be due to defects in repair or variability in the efficiency of DNA repair. So, we are really interested in all of these issues that shed light on the issue of susceptibility. A greater understanding of issues related to susceptibility will improve our ability to relate exposure to disease outcome, and predict which population, which individuals, would be at greater risk.

Real quickly, I would just like to throw up a couple of lists that are very specific to the Love Canal. Perhaps many of you have seen this before. This is a list of many of the substances present at the Love Canal and illustrates the problem that a toxicologist or epidemiologist has in assessing health risk. Again, we have a very complex mixture of substances that were placed there and again, the quantities of some of these are huge. One of the big ones was lindane—6,900 tons were estimated as being dumped in the Love Canal. This list includes the quantities of chlorinated aromatic substances that were actually found in the Love Canal. You can see that the media that were extensively studied were water and leachate leaving the area and air and soil/ sediments. Again, the greatest potential for human exposure were probably the kids that were exposed to soil and sediments. Soil and sediments have the highest levels, the highest concentrations of most chemicals. But again, even though they were perhaps eating the soil or playing in the soil, the question was how much was actually being absorbed? What was the internal dose? What was the potential to biodegrade these chemicals in the soil?

This table includes a substance that during the late 1970s, and really for the next twenty years, has been what people refer to as the toxin of the decade. It is probably the toxin of the century, that is dioxin (TCDD). Unfortunately, dioxin was one of the substances found in the Love Canal. Dioxin was an unwanted waste material associated with the synthesis of chlorinated phenolic materials. As a result of chlorine chemistry by local industry, dioxin was deposited in the Love Canal.

What I would like to do is digress a little bit to show you where we have come since the Love Canal regarding our knowledge regarding dioxin. There was a time during the late 70s and early 80s [where] there was heightened concern about dioxin. In the toxicology literature, it was touted as the most potent man-made substance known. Again, the mere fact that dioxin could be found at a residential site was quite alarming. This fact in itself was something that the residents could really grab a hold of and say, "I've gotta get out of here. There is dioxin on my property." But, again at that time we didn't know too much about the health effects of dioxin except for the wide range of potential adverse effects associated with dioxin.

First of all, maybe I should show you a little bit about what we mean by dioxin. These are some chemical structures and in the upper left hand corner is the structure of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin). Again, TCDD or dioxin has chlorine in essentially the corners of the planar molecule. You can see that all of these other structures are similar, some of these are chlorinate biphenyls (PCBs), others are chlorinated dibenzofurans. They all have a similar structure and they all have varying potencies with, unfortunately, the compound in the upper left hand corner which is generally referred to as dioxin, being the most potent of all these substances. If we look at data on chlorinated dioxins and the structurally related dibenzofurans, they were found in the soil of the Love Canal. The concentration of 38 parts per billion (ppb) for 2,3,7,8- TCDD, stands out as the substance that had the highest concentration of all of the other penta, hexa, hepta and octa-chlorinated dioxins and dibenzofurans.

This is a very unusual profile. Normally the levels of TCDD would be less than 3 parts per trillion (ppt) but since it had a level of 38 ppb, it really stuck out. It really became pretty clear that this most active, most potent, of all the chlorine dioxins was the principal unwanted dioxin-like contaminant that was left at the Love Canal and was found in much of the soil in the region. Again, that resulted in a great deal of concern and probably much testing. This is just one figure I saw that shows some [of] the levels that were found. Again, these levels are in parts per billion (ppb).

PPB refers to parts per billion, which is a term that toxicologists waved around quite a bit. A part per billion is a thousand times more than a part per trillion. It is the concentration of dioxin on a weight per weight basis. You can see that in general when you are looking at water the levels are much lower compared to say an organic substance such as soil or sediment, which has much higher levels. But, the point of this is that there is testing throughout this whole area, with the hatched area being the actual canal. You can see that there were measurable levels of dioxins throughout the whole region. The number that was always a concern is really one part per billion and anything above one part per billion is considered to be a highly contaminated region. So, these part per trillion levels, yeah, that's a concern, but dioxin in soil at one part per billion is considered an action level that needed remediation.

So, what do these levels mean? I think that is what the bottom line is from the toxicology point of view. What do these levels mean with regard to human health? The EPA, over the last twenty years, [and] researchers have been collecting data trying to put into perspective what these levels of dioxin mean regarding adverse health effects. Hopefully in the next few months the EPA will finally release a document that is a health assessment document on dioxin which is trying to really put into perspective what the real risks are for dioxin to human health.

I am going to share a few points with you. Chloracne at the time of the Love Canal, this severe form of acne, was thought to be the ultimate human marker of dioxin exposure. What types of levels were needed to see chloracne? Well, from the scientific literature on this topic, it appears that anywhere from 45 to 3,000 nanograms per kilogram of body weight. That is the dose of dioxin that was needed to elicit a response, which is chloracne. You can see there is a big range for human susceptibility. Some people respond to really low doses, while others respond to much higher doses. The next table summarizes data not only from humans where we have estimates of what dose produces a given response, but looks at other animal models to see what doses elicit those responses in animals. You can see that the list of endpoints for dioxin is remarkable. The wide range

of potential adverse effects associated with exposure to dioxin fueled a lot of people's concern about chemicals like dioxin. Dioxin has a potential to elicit adverse health effects such as cancer, immunosuppression, decreased birth weight, developmental delays, and effects on objective learning in monkeys.

The study by Schantz and Bowman is striking in that a dose or body burden of dioxin as low as a concentration of 19 nanograms per kilogram of body weight could elicit effects on learning in monkeys. Keep that number in mind—19 ng/kg of body weigh—because I am going to show another table. Cancer at the time of Love Canal was the big endpoint that everyone was concerned about. What really has changed over the last twenty years is that we are looking more closely at other more subtle effects than cancer. You can see that rather than nineteen parts per trillion (19 ng/kg) for adverse effects on learning, it may require a body burden of dioxin from one hundred to seven-thousand part per trillion to elicit cancer in humans. Today we know that dioxin is a known human carcinogen. We didn't know that ten years ago. So, we have made some strides. We do know more about substances like dioxin because it's gotten a great deal of notoriety particularly over the last twenty years.

One of the more interesting observations that has been reported in a couple of the human studies is the effects of dioxin exposure on glucose tolerance and glucose metabolism and other endocrine related effects. These are seen at some extremely low levels. The Wolfe study was in a group of Vietnam veterans that served in Operation Ranch Hand. The Sweeney study was in an occupational cohort. Studies with very low levels of dioxin exposure were reporting effects on glucose metabolism, and serum testosterone levels. These studies are indicative of the endocrine disrupting effects of dioxin. So it is not chloracne, but cancer, and subtle neurobehavioral and endocrine disrupting effects that we need to be more concerned about.

Finally, the last overhead I will put up looks at what the background levels of these chemicals are in humans? It is estimated that a background level of dioxin-like chemicals in humans is about 9 nanograms of dioxin per kilogram of body weight. From the earlier

brief review of adverse health effects associated with low level dioxin exposure, it is possible that we may detect subtle adverse effects at dioxin body burden levels that are just above the normal background level. I am not trying to alarm you, but I am just trying to suggest that public health policy should be prudent and any excess exposure to dioxin should be limited. I am not saying that we are all doomed to develop reproductive or developmental effects or other adverse effects from dioxin. What I am saying is that we all do have a background level of this substance. Therefore it is prudent to keep that level as low as possible. I guess that is something that wasn't a mistake at the Love Canal—they did take action regarding the dioxins present there. Sound public health policy will dictate that we continue the very vigilant effort to limit our exposure to substances, such as dioxins, that have such a wide range of potential adverse outcomes.