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Agent Orange and the Challenge of Assessing Toxicity - Part 3

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This is the third part of the Agent Orange series. Part 1 discussed the make-up of the two herbicides that go into Agent Orange, and Part 2 covered the chemistry that led the formation of toxic dioxins in Agent Orange during manufacture. This part will cover the toxicity of the 2,3,7,8-TCDD in Agent Orange and why it is still of concern.

Before we get into the toxicity of 2,3,7,8-TCDD and Agent Orange, let's go into the basics of risk assessment. Just because something is known to be toxic does not mean we need to worry. Assessing the risk means we need to assess several key factors first.

For example, as we all know, we depend on water for our health and functioning such that we cannot survive for long without water. However, if drunk in sufficiently large amounts, water can be toxic because sodium in your body becomes diluted to the point where you cannot function. Obviously, drinking such large quantities of water is not a concern for most of us, so we know that drinking water has low risk most of time, and is in fact highly recommended.

So when assessing risk of potentially toxic substances, scientists and medical workers tend to take into account three important and connected concepts:

- **Hazard** – what are the hazards of this substance? For example, would it result in allergic reactions, illness or burns on exposure?
- **Exposure** – What are the routes of exposure? Would it be inhaled, eaten, or absorbed through the skin? How much of this substance is being would be transferred through exposure?
- **Toxicity** – what is the mechanism of toxicity after exposure? How does the toxicity response show up?

So drinking freshwater water has low risk, due to its low hazard and toxicity only incurred to very high exposure through drinking. Of course, water can be very risky in other settings, such as slipping on a puddle on a marble floor and breaking your hip, or drowning in the bathtub.

In terms of toxicity, 2,3,7,8-TCDD is quite the opposite of drinking water, and avoidance of this substance is highly recommended by all experts. So how is it so toxic?

We'll be delving into biochemistry in this posting this time! In brief, the toxicity of 2,3,7,8-TCDD is due to its ability to bind with a key receptor in our cells, which leads to a cascade of effects. As a part of our healthy cell functioning, there are thousands of *receptors* in our cells throughout our bodies which act as our messenger system.

The receptors bind to key chemical molecules. Usually, they are made of proteins with certain structures that enable chemical bonding on its surfaces in a manner often described as "a lock and a key". Once a receptor is paired with its "chemical key", it then can influence the DNA expression within a cell. This helps to organize useful chemicals to enable healthy cell functioning.

In the case of 2,3,7,8-TCDD, scientists are the most concerned with **Ahr**, or the **Aryl hydrocarbon receptor**. It has been speculated that the Ah receptor may be a relic of from our long-past evolutionary history, with its "key" being a growth-regulating hormone which we no longer use. The Ah receptor is not only found in humans but also in numerous animal species. The Ah receptor in modern organisms now binds naturally occurring organic contaminants such as those produced by combustion of wood. In fact, dioxins are only toxic when the Ah receptor is involved!

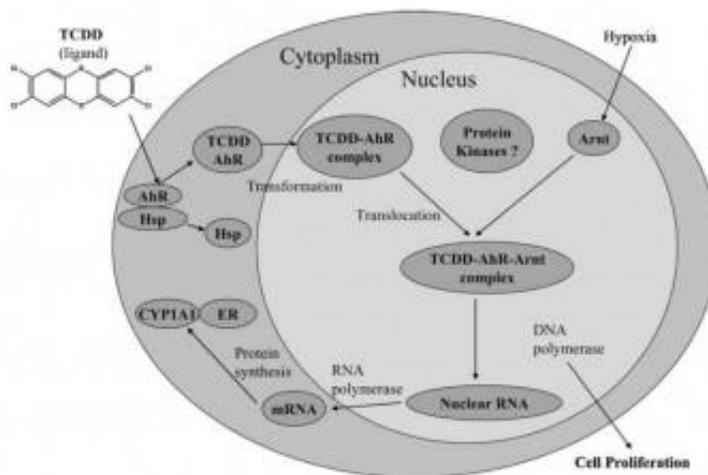
The Ah receptor will bind with organic contaminants containing a 6-carbon hexagon ring. Once the Ah receptor binds with an organic contaminant, the Ahr-contaminant complex moves to the cell nucleus where DNA genes are activated. Enzymes are produced to break down the unwanted contaminant and remove it from the cell. In this case, this involves a group of enzymes called the cytochrome P-450. If all goes well, those enzymes activate a reaction to break down the contaminant in the cell, and therefore helping to remove the toxic substances from the cell and the body.

In this case, 2,3,7,8-TCDD has been found to bind with the Ah receptor extremely well. In fact, 2,3,7,8-TCDD has the best binding constant with the Ah receptor among the various organic contaminants, explaining its extreme toxicity. It has been hypothesized that the 2,3,7,8-TCDD may be very similar in structure to the original hormone partner of the Ah receptor before we lost this hormone a long time ago in our evolutionary history.

After exposure and uptake, the 2,3,7,8-TCDD-Ahr complex will then proceed to the DNA in the cell nucleus, where activated genes will result in (1) production of the P450 enzymes; and (2) regulatory chemicals important for growth and division of cells. In some ways, the dioxin mimics the behaviour of hormones regulating important cell functions. Also, it is thought that by binding with the Ah receptor for too long, it could result in the wrong signals being sent out during development, resulting in birth defects and developmental delays after birth.

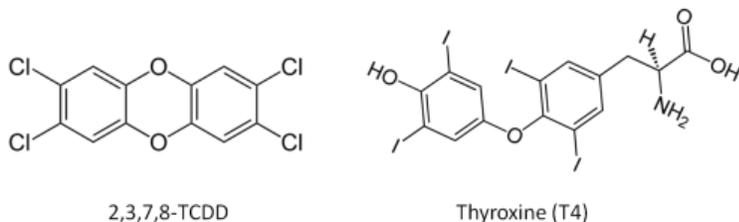
Those two actions will lead to a cascade of effects throughout the cell and the affected organ. First, due to the high affinity of 2,3,7,8-TCDD for the Ah receptor, sometimes the dioxin is not broken down. Therefore, P-450 enzymes are produced in the cell for an extra-long time. All those extra enzymes does not break down the dioxin immediately, but it can lead to the breakdown of other hormones. The breakdown of regulatory hormones can lead to dysfunctional cells and promote cancer. Down below is a figure that illustrates the pathways within a cell:

Fig. 3 Simple mechanistic model for TCDD toxicity using the AhR pathway. ER endoplasmic reticulum, CYP1A1 cytochrome P450 1A1, AhR aryl hydrocarbon receptor, Hsp heat shock protein, Arnt Ah receptor nuclear translocator, mRNA messenger ribonucleic acid



Dioxin and Ah receptor cascade from Mandal (2005)

Second, the Ah receptor has other functions beyond enzyme induction. It can control certain genes and cell functions particularly those governing growth and differentiation. As an example, 2,3,7,8-TCDD is somewhat similar to an important thyroid hormone, the thyroxine, as shown below:



As a result, 2,3,7,8-TCDD may mimic certain hormones after binding with the Ah receptor. Since hormones do not act alone, this interaction of dioxin hormone mimics with hormones can result in a cascade of effects throughout the body.

There has been many studies showing that certain cancers and diseases respond with increasing exposure to dioxins. But it has been difficult to precisely pin down the association due to the complex biochemistry and the cascading domino effect whenever hormonal systems in cells are affected.

So what? The discovery of dioxins in Agent Orange and the subsequent explosion of biochemical and environmental research into dioxins world-wide has led to our much improved understanding of organic contaminants, their toxicity and the need to better regulate and monitor those contaminants.

Should we be worried? Yes. 2,3,7,8-TCDD is one of the most toxic compounds people have ever produced due to its ability to bind so strongly to the Ah receptor found in numerous organisms. But there are good news.

Over past 50 years, as our awareness of environmental contaminants and management of sources improved, the release of dioxins to the environment and the accumulation of dioxins in wildlife has been steadily decreasing. As a population, our overall environmental exposure is decreasing on average.

However, dioxins are persistent in the environment, often present for decades. Scientists can still measure dioxins in lake sediments from the 1950's! Dioxins also can accumulate in fatty tissues and in soil, where they can be transferred up the food chain. As a result, exposure to dioxins can include both immediate exposure to the chemicals such as Agent Orange, and long-term exposure through food and skin contact from accumulated dioxins in the environment. This further adds to the complexity of understanding dioxin toxicity and relating health concerns with environmental exposure over a long period.

However, remember that risk assessment of a chemical depends on three things, hazard, toxicity and exposure. The extent of toxicity and health impacts depends on the length of exposure and how people were exposed. As a result, the occasional driver who drove by Ontario's highways during spraying have far less to worry about compared to the highway workers who sprayed Agent Orange on unwanted foliage. However, showing causation and relationship between current health issues to past dioxin exposure is exceedingly difficult even for exposed workers. We are exposed to so many organic contaminants which also trigger the Ah receptor cascade, and each of us respond differently depending on our genetic make-up. Despite over 50 years of research, there is still much that needs to be unravelled.

References & Resources:

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