POTENTIAL ADVERSE EFFECT OF ENDOCRINE DISRUPTORS AT LOW DOSES

Milena Stošić[1*], Sanja Veselić[2], Branko Vidicki[3]
[1]Faculty of Technical Sciences, Department of Environmental Engineering, University of Novi Sad, Serbia
[2]Faculty of Natural Sciences, Department of Biology and Ecology, University of Novi Sad, Serbia
[3]Faculty of Agriculture, University of Novi Sad, Serbia
*e-mail: MILENA.STOSIC@GMAIL.COM

ABSTRACT

Chemical pollution, acute and chronic, can present a serious threat to living organisms, their health, and their biodiversity. Intensive use of pesticides has resulted in their presence in water, soil and air. Number of these chemicals can act as endocrine disrupting compounds, cause pollution of natural ecosystems and can adversely affect species diversity. Endocrine disrupting chemicals are emerging risk for human health and the environment. What makes endocrine disruptors so significant is that they are often more active at lower doses, far beneath of those which are traditional concern to toxicologists.

INTRODUCTION

The very important question of today's life is regarding organic chemicals used in pesticides and if they are putting people and wildlife in risk by interfering with their endocrine system. It is possible to detect the presence of measurable levels of several hundred synthetic chemicals in every living person. Those contaminants didn't exist prior to 20th century, but even though we are living in 21th century, we are still ignorant about the health impacts and interactions of most of these compounds.

Endocrine disrupting chemicals (EDC) are emerging risk for human health and the environment. Endocrine disruption is a relatively unstudied area in toxicology and is only recently being taken into account in risk assessment [1]. Unlike carcinogens and other toxins, government agencies were not designed to regulate EDCs, which are much more complicated and difficult to understand [2]. EDCs are toxic because they disrupt the normal function of the endocrine system. By interacting with hormone receptors, they prevent endogenous hormones to bind with them and induce biological effect. Standard tests used by the EPA to evaluate reproductive and developmental toxicity often fail to consider the impact of doses lower than those producing no evidence of overt adverse effects, described as the no-observed-effect level, or NOEL.

Some endocrine disruptors exhibit dose-response relationships described as nonmonotonic, meaning that within a certain dose range, a chemical's effects on a given end point actually become greater as the dose is reduced [3]. The endocrine system involves a myriad of chemical messengers and feedback loops. Often, the endocrine system does not respond to chemicals in accordance with the canons of traditional toxicology. In toxicological studies, the failure to apply fundamental principles of hormone receptor biology to dose selection can potentially lead to a huge error in estimating risk associated with exposure to doses below the

NOEL determined in traditional toxicology studies [1]. These issues are problematic for toxicology because they challenge the traditional use of extrapolation from high-dose testing to predict responses at much lower environmentally relevant doses. Additionally, these data also provide evidence that some traditional assumptions used in risk assessment for systemic (noncancerogenic) toxicants, such as the assumption of threshold and monotonic dose-response relationship can not be uniformly applied to EDCs [1].

It is very important to understand the link between sources of pollutants and health effects. Chemical pollution, acute and chronic, can present a serious threat to living organisms, their health, and therefore, their biodiversity.

There exists little doubt that the biological diversity is being rapidly depleted as a direct and indirect consequence of human actions. Intensive use of conventional pesticides, as well as the presence of variety of manufactured products in wide usage including plasticizers, flame retardants, and various industrial chemicals, can lead to biodiversity decline.

Since endocrine disruptors are emerging risk for environment, wildlife, and human health, manny of these chemicals are classified as emerging substances of concern by NORMAN project [4].

LOW DOSES NON-LINEAR RESPONSE CURVES

What makes endocrine disruptors so significant is that they are not bound by the classic assumption that by lowering the dose, we decrease the toxic potential of the chemical. The threshold-based system of determining chemical toxicity, used in regulations and industry, is simply not capable of protecting from endocrine disrupting chemicals [5].

The relationship between low doses and risk may not always be linear. Major errors in assessing risk can be made when linearity of response and the preceding receptor occupancy is assumed across the entire dose range, which is the current assumption used in risk assessment [1]. Government Agencies often find crafting the proper regulations difficult, given the fact that most toxins, including EDCs follow a U- or J-shaped curve, depending on whether the substance causes a decrease in risk or an increase (Fig.1.) [6]. Toxicologists now believe that exposure to toxins at very low or very high levels has more adverse affects on homeostasis then mid-level exposure rates [2].

This combination of low-dose stimulation followed by high-dose inhibition is commonly termed "hormesis". Hormesis is not new concept, and it has been in use for long time by those studying epidemiology and molecular pharmacology, but it was ignored by toxicology community until relatively recently [6]. Hormetic effects are difficult to measure and quantify without extensive studies using many animals, and are not frequently seen in experiments designed by toxicologists who are more interested in upper end of dose response curves, where dose and risk are at their highest [6].

There are some strong advocates of the U-shaped dose-response curve who think that there should be a paradigm shift in toxicology [7, 8]. The old paradigm focused on acute toxicity. The new paradigm recognizes that there are other ways that contamination can work [9]. The implications of this new paradigm are profound. Toxicologists used to believe that background levels, levels experienced by most people, the levels that are unavoidable living in the world today, were safe. That assumption of safety was allowed because scientists were considering them under the old paradigm [2]. Endocrine system is complex, and regulation of EDCs can become complicated because lowering the exposure levels may, in fact, increase the health and environmental risks. Additionally, reaction to unequal concentration levels may be different in different stages of development [2].

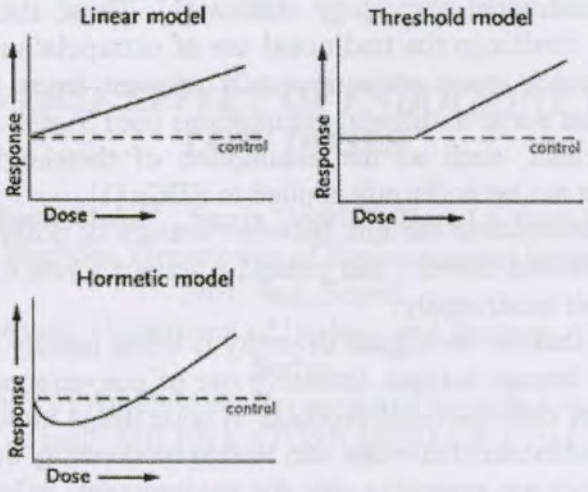

Fig. 1. Dose–response relationships (12)

The toxicological approach involves dose-selection based on the maximum tolerated dose, which can be described as "top-down dose selection", whereas the physiologic approach used by Nagel et al. (1997) [10] can be described as "bottom-up dose selection" [11]. Vom Saal and Hudges (2005) [11] showed that there is now overwhelming evidence demonstrating that different experimental approaches lead to very different conclusions of safety regarding the reference dose for Bisphenol-A of 50 μg/kg/day. Findings based on low dose studies thus present a strong challenge to the assumption that form the basis for chemical risk assessments [11].

CONCLUSION

- Endocrine system is very complicated and it is becoming more and more obvious that traditional toxicology assumption that dose - response curves are always monotonic can not apply anymore. High doses can, sometimes, block effects that occur at lower levels. This is very common with endocrine disrupting chemicals, which is why the dose - response curves for EDCs are not linear.
- It is an imperative for policymakers and agencies to deal with the toxicology implications of new and complex chemicals. Techniques used to deal with toxic chemicals are inadequate and will be more and more inappropriate when more chemicals are discovered to have endocrine disruption effect.
- Low doses of hazard chemicals in level of ppb and ppt are registered to have negative effect on biodiversity and changing environment. Low doses effect may be explained by presence of free molecules, not associated in clusters, but with free active center and therefore with maximal activity.

REFERENCES

[1] Welshons, W., Thayer, K., Judy, B., Taylor, J., Curran, E., vom Saal, F. (2003). Large effects from Small Exposures. I. Mechanisms for Endocrine Disrupting Chemicals with Estrogenic Activity. *Environ Health Perspect*, 111, p. 994-1006.

[2] Gitanjali, D. (2005). Endocrine Disruptors: A Case Study on Atrazine. *Temp. J. Sci. Tech. & Envtl. L.*, p. 397-418.
[3] Schmidt, C. (2001). The low-down on low dose endocrine disruptors - NIEH news. *Environ Health Perspect,* 109, p. 420-421.
[4] http://www.norman-network.net/index_php.php
[5] Pullin, A. (2002). Conservation Biology, Cambridge University Press, Cambridge.
[6] Hadley, C. (2003). What doesn't kill you makes you stronger. *European Molecular Biology Organization*, 4, p. 924-926.
[7] Calabrese E., Baldwin, L. (2003). Hormesis: The Dose-response Revolution. *Annu Rev Pharmacol Toxicol,* 43, p. 175-197.
[8] Krimsky, S. (2000). Hormonal Chaos. Johns Hopkins University Press.
[9] http://www.ourstolenfuture.org/newscience/lowdose/lowdose.htm
[10] Nagel, S., vom Saal, F., Thayer, K., Dhar, M., Boechler, M., Welshons, W. (1997). Relative binding affinity-serum modified access (RBA-SMA) assay predicts the relative *in vivo* bio-activity of the xenoestrogens bisphenol A and octylphenol. *Environ Health Perspect*, 105, p.70–76.
[11] vom Saal, F., Hughes, C. (2005). An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment. *Environ Health Persp,* 113, p. 926-933.
[12] http://www6.ufrgs.br/favet/imunovet/molecular_immunology/generaltoxicology.html