

EDITORIAL

Why research on Endocrine Disrupting Chemicals is still worthwhile

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Endocrine Disrupting Chemicals (EDC, see the dedicated web area <http://www.iss.it/inte>) can damage human and/or animal health by altering the hormone function(s). The endocrine system is the most complex signalling network in the organism; EDC, therefore, may act through a number of mechanisms and targets. Accordingly, EDC are a wide and diverse group including e.g., pesticides, plasticizers, persistent pollutants, natural plant metabolites.

EDC represent a long-standing concern for international agencies involved in the risk assessment of chemicals, as well as an issue for intense debate among scientists, industries and the public. From the toxicologist's viewpoint, such debate is not pointless at all. EDC are hazardous for next generation's health, since hormones are crucial for development, from embryo through to puberty. Each hormone regulates several organs and tissues, thus an EDC can hit several targets. For instance, experimental studies on the plasticizer bisphenol A, considered as an "estrogen-mimicking" EDC, have identified multiple targets in developing rodents, such as mammary gland, liver, brain, reproductive and immune systems. The susceptibility to such effects may also change depending on the sex-related endocrine regulation. Last but not least, EDC are widespread in environment, products, foods and some may also bioaccumulate: thus, EDC pollution may lead to cumulative exposures to chemicals sharing the same targets.

Europe and some Member States have devoted substantial resources to research on EDC for about twenty years. Thus one EU citizen could legitimately say "So much knowledge gained, stop putting money on research, let's regulate the hazards": my answer is "Yes and No".

"Yes" because gaps of knowledge must not prevent taking action whenever it is supported by knowledge. For instance, current EU regulations on pesticides and biocides require that EDC are identified and restricted: the available knowledge does allow to identify substances as EDC, thus, delays would be unjustified.

"No" because the available evidence presents several gaps which are definitely relevant for building-up a science-based risk assessment.

The first one is an old, yet still ongoing, story. How can we define a "safe dose" for EDC? EDC that inter-

act with nuclear receptors may elicit a cellular response at very low doses, which may be qualitatively different from that elicited at higher doses (e.g., stimulating at lower and antagonizing at higher concentrations): research is still needed to understand whether these low-dose responses are linked to adverse effects, especially in developing organisms which are considered to be more susceptible. The characterization of dose-response relationships is one pillar of risk assessment: should this framework be modified to take into account EDC low-dose effects? And how?

Then, are we able to assess hazards to all main EDC targets? Most EDC research still concentrates on effects on the reproductive cycle, whose importance cannot be disputed. Yet, as already mentioned above, major hormones do regulate a number of organs and tissues, including some (e.g., bone) that are not usually investigated in toxicological testing. The hormone balance is paramount to regulate the complex process of neurobehavioral development: yet, efforts are still required in order to translate research findings into reliable parameters to assess the neurodevelopmental impact of EDC. Even more important, the current testing tools do not appropriately identify effects related to the major, endocrine disease of today's world, type II diabetes; the same applies to the endocrine component of obesity, which is connected to diabetes in the so-called "metabolic syndrome". Experimental, and to a lesser extent epidemiological, research shows that some environmental chemicals increase the risk of diabetes and/or obesity; in general such substances belong to the small group of thoroughly investigated "usual suspects", like arsenic or bisphenol A. The absence of robust endpoints and assays jeopardizes the consistent identification of substances that elicit effects relevant to such top-class public health issue as the metabolic syndrome. Adverse outcome pathways (AOP) are a novel toxicological approach, building causative chains from initiating events at molecular level through cellular changes that reflect the onset of adversity up to pathological conditions at tissue and organism level. Indeed AOP could support understanding of the full spectrum of EDC effects.

Identified or potential EDC are present in our living environment. Is there a health risk ongoing? Should urgent measures be taken to reduce such risk? Research

needs on EDC include epidemiological studies, which currently show a good ground for improvement. A major issue may be how to assess the “early exposure-late effect” scenario which is the foremost EDC-related health problem. In practice, the previous exposure in the womb or during early childhood does matter more than the current EDC level in body fluids of fully-grown adults. How to cope with epidemiological investigations about the EDC impact on developmental programming? An answer could be creating and exploiting biobanks, and finding predictive biomarkers of effect that can link developmental exposures to adult health risks. Not to hint that adult exposure does not matter: here too, substantial advances are needed, including models and tools for exposure characterization and relevant biomarkers. Biological plausibility of endpoints and findings is a main requirement for epidemiological studies: “cross-fertilization” between epidemiology and toxicology will greatly help. Finally, and again, also epidemiological research should take into account substances other than the “usual suspects”.

All that said, many EDC are useful substances for consumers, not just for industry: pesticides to support farming, plasticizers, preservatives, sunscreens, flame retardants, etc. Yet, restrictions are required to protect human health and environmental integrity. Substitution of high-concern substances, including EDC, is invoked by the European Regulation REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals). Candidates for replacing high-concern substances might just appear to be less hazardous because their toxicity has been insufficiently investigated. The challenge, therefore, is to develop robust approaches to identify safer substitutes for EDC of priority concern; this requests the development of time- and cost-effective screening strategies, making the best possible use of non-animal (*in silico*, *in vitro*) tools (see the project LIFE EDESIA, <http://www.iss.it/life>).

So, we do not need just “more research” on EDC; rather, we need “fit-for-purpose” research to support risk managers and policy makers in Europe and worldwide.