

COLLEGIUM RAMAZZINI

ENDOCRINE DISRUPTING CHEMICALS IN THE EUROPEAN UNION

The Collegium Ramazzini is an international scientific society that examines critical issues in occupational and environmental medicine with a view towards action to prevent disease and promote health. The Collegium derives its name from Bernardino Ramazzini, the father of occupational medicine, a professor of medicine of the Universities of Modena and Padua in the late 1600s and the early 1700s. The Collegium is comprised of 180 physicians and scientists from 35 countries, each of whom is elected to membership. The Collegium is independent of commercial interests.

ABSTRACT

Europeans are exposed to Endocrine Disrupting Chemicals (EDCs), both natural and synthetic, to an extent that is causing adverse health effects. They include serious conditions like testicular, breast and prostate cancers, decline in sperm counts, pregnancy loss, puberty abnormalities, reproductive organ deformities, neurological problems, diabetes and obesity. Recent research suggests that the EDC effects can even be transmitted to future generations. The Collegium Ramazzini therefore urgently calls for new ways to test chemicals and to revise current approaches to risk management. In regard to the REACH authorization, the Collegium Ramazzini recommends improved test protocols and expanded test requirements to allow identification of EDCs, for which a safe threshold cannot be determined at present. Thus, the scope of REACH art 60(3) should be extended by default to all EDCs as substances of very high concern. Stringent hazard based cut-off criteria must be used for EDCs. In this process, GLP studies should not be considered the only basis for risk assessment, which must consider all academic research of high quality. Only in this way can the EU satisfy the requirement for a precautionary approach that will protect the general population and workers against these serious hazards.

STATEMENT

Endocrine disrupting chemicals (EDCs) are synthetic or natural compounds that can cause disease and dysfunction by interfering with the action of the natural hormones in the human body that regulate growth, development, reproduction and aging and influence risk of cancer. Examples of synthetic EDCs include phthalates, bisphenol A, perchlorate, certain pesticides, brominated flame retardants, certain metals and dioxins. Chemicals with endocrine disrupting properties are manufactured in volumes of millions of tonnes per year and are widespread in consumer products such as soaps, shampoos, perfumes, electronics, textile and foam furnishings and plastics. They are common contaminants in air, food and drinking water. Evidence grows that exposure to EDCs in the places that we work, learn, live, and play is significant. National biomonitoring surveys document that that we all carry EDCs in our bodies.

The body of evidence on the health impacts of endocrine disrupting chemicals (EDCs) is substantial and increasing. Several recent reports have summarized the known and likely effects of these chemicals which include increased risks for testicular, breast and prostate cancers, decline in sperm counts, feminization *in utero* of newborn baby boys, pregnancy loss and

shortened gestational age, early puberty, reproductive organ deformities, neurological problems, diabetes and obesity. Early life stages including fetal, neonatal, and childhood development are particularly vulnerable to EDCs. Exposures in early life to EDCs can trigger onset of diseases in childhood and also later in life. EDC exposures can also affect the subsequent generations by causing alterations in gene expression in germ line cells (eggs and sperm).

The European Union (EU) is currently revising its EDC strategy. The European Parliament has voted a Resolution stressing the need for prompt action to protect public health, in accordance with the precautionary principle, and asked for reduction of exposure and improvements in the EU regulatory system. Several EU member states have already banned or announced intentions to ban certain uses of EDCs. These decisions to protect public health have been made on the basis of existing science. Currently criteria for identifying and assessing EDCs are under development and should apply across all relevant EU laws. The mandate to develop these criteria is given in the pesticides and biocides regulations (Regulation 07/2009 and 528/2012), and the Criteria must be proposed (for pesticides) or adopted (for biocides) by December 2013. The Pesticides and Biocide laws include a cut-off scheme that eliminates EDCs (with certain exemptions). Also, the review of how the substances should be treated by the REACH authorisation process requires a decision on whether a threshold level for effects can be determined for EDCs or not. If an expansion of the scope of REACH article 60(3) to include EDCs seems justified, authorisation for the use of EDCs identified under REACH can be granted only if it can be demonstrated that the socio-economic benefits outweigh the risks to human health, or the environment, and if there are no suitable alternative substances or technologies.

In view of these policy opportunities and the need for action, the Collegium Ramazzini recommends the following:

Improve Testing Protocols and Testing Requirements. As recently concluded by the WHO/UNEP, the internationally agreed and validated test methods capture only a limited range of the known spectrum of endocrine disrupting effects and are inadequate to detect endocrine disrupting effects that are linked to many human diseases. This increases the likelihood of harmful effects in humans and wildlife being overlooked. Further testing will be needed to identify biologically significant effects including low dose effects, effects from early life-stage exposures, non-monotonic dose response curves, impact of chemical mixtures, or behavioral and cognitive effects that are often missed with traditional toxicity testing. The testing requirements of EU legislation would need to be expanded so that adequate data are generated. Such data needs will likely require both animal testing and use of alternative methods. Sprague Dawley rat models, which are already in use for carcinogenicity bioassays and for the Endocrine Disruptor Screening Program of the EPA, seem to be particularly appropriate. A more realistic risk assessment should include prenatal exposures and prolonged observation of experimental animals at least up to 130 weeks.

Include Academic research as a basis for risk assessment. Government and public health agencies should not rely only, or even preferentially, on GLP studies. The selection of evidence for good quality risk assessment by government and public health agencies must include academic research, published in respected scientific journals after a peer-review process and publicly accessibly, in addition to consideration of studies conducted according to established “Good Laboratory Practices” (GLP) criteria.

It is important to recognize that GLP requirements are merely *de minimis* criteria and not a seal of scientific excellence. They are designed to set a baseline of cleanliness, animal care, and record-keeping. They are not associated with higher quality research, proper study design or correct statistical analysis. In fact, GLP study designs are often very outdated and do not reflect the current science, most sensitive disease endpoints, or chronic disease outcomes. In contrast, most academic research reflects current scientific advances, has been published in respected scientific journals and relies on the peer-review process and public accessibility to uphold scientific quality.

Extend the scope of REACH art 60(3) by default to all EDCs identified as substances of very high concern. EDCs are to be regarded as substances for which it is not possible to determine a safe threshold for adverse effects and adequately control the risks. They have been shown capable of causing injury to the developing human brain and reproductive organs at the lowest levels detectable, levels far below those that harm adults, particularly if the exposure occurs during a critical developmental window. Unlike traditional environmental toxicants in which the risk of adverse events increases as the exposure levels increase, endocrine disruptors may exert effects at both low doses as well as high doses.

Define strict cut-off criteria, based on hazard assessment. Deriving an exposure dose that may be considered safe and assessing risk cannot be carried out with a satisfactory level of certainty due to the occurrence of adverse effects at low doses; the existence of non-monotonic dose response curves; co-exposures to a whole range of chemicals which may affect the same adverse outcome; irreversibility; exposure during critical stages of development; and of early life exposure and onset of diseases later in life. Therefore stringent hazard based cut-off criteria for identifying and assessing EDCs are justified.

Apply the precautionary principle and respond to early warning signals. The precautionary principle provides justification for acting in the face of uncertainty, as a tool for acting on the basis of early warnings. While support for targeted research is a high priority, the need for further research should not delay necessary policy and regulatory decisions to protect public health. Accordingly, technologies are no longer presumed safe simply because evidence of risk or adverse effect is unavailable. Precautionary approaches presume that an induced adverse response in animals is a reliable indicator of potential harm in humans, unless informed otherwise by multiple well-designed and well-conducted studies. The EU Treaty includes the precautionary principle. Also the World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) from 1995 allows provisional measures “on the basis of available pertinent information.

Reduce exposure. The possible public health implications of exposures and the uncertainties in risk assessment as mentioned above highlight the need to reduce exposure to EDCs and to replace them with safer alternatives whenever available.

Monitor exposure. Monitoring of the general population, workplaces and workers in the EU for exposure to EDCs and for possible effects should support and evaluate regulatory control measures. Recent human biomonitoring studies from across Europe addressing a limited number of biomarkers have shown EDCs in both children and their mothers.

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