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AOP AS A TOOL FOR THE CLASSIFICATION OF SUBSTANCES AS ENDOCRINE DISRUPTOR: THE CASE STUDY OF BISPHENOL A : EFFECTS ON THE FEMALE REPRODUCTIVE FUNCTION

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According to EU REACH legislation, endocrine disruptor (ED) substances are to be identified as Substances of Very High Concerns (SVHC) which can ultimately lead to the progressive substitution of those substances. The European Commission's Endocrine Disruptors Expert Advisory group agreed in 2013 on the elements for identification of an endocrine disruptor, in line with the WHO definition. To be classified as an ED a substance has to show endocrine mode of action (MoA), adverse health effects in individuals and/or their offspring or in population and most importantly the link between the adverse effects and the endocrine MoA has to be clearly established. Given the multiple and critical roles of the endocrine system to maintain the homeostasis of pretty much all biological processes in living animals and the multiple pathways and mechanism it can trigger to reach this goal, demonstrating that a given substance or mixture is an endocrine disruptor according to the EU criteria constitutes a huge challenge for the scientific experts involved in regulatory toxicology. Clear-cut epidemiological data linking exposure to EDs and adverse health effects are scarce. This is largely intrinsically linked to the specific characteristics of the endocrine disruption action. It is because the disorders induced by the EDs are delayed and multifactorial, and because we are exposed to hundreds EDs with synergic, additive or subtractive effects (cocktail effects), that most of the epidemiological studies researching an association between the exposure to one ED and the development of one disease fail to be conclusive. Experimental studies in which both adverse effects and endocrine mode/mechanisms of actions are simultaneously addressed are very difficult to design and perform as they would require a whole battery of both in vivo and in vitro/silico approaches and, as so, remain very scarce and limited. Therefore, Adverse Outcome Pathway construct might represent a very valuable tool for the scientific experts to determine if a substance should be considered as an endocrine disruptor. Herein, we report the AOP construct that was build and used by ANSES's Working Group on "Endocrine disruptors" (WG ED) to evaluate bisphenol A as an endocrine disruptor targeting the female reproductive system. In relation to alteration of estrous cycle as an adverse effect, a clear endocrine MoA could be drawn from experimental in vitro and in vivo data in schemes of adult exposure. It implied modification of ovarian steroidogenic activity and more particularly alterations of aromatase activity. Alteration of cycle further to a developmental exposure to BPA through endocrine or neuroendocrine mechanisms is less clearly demonstrated. Nevertheless, many studies show that the basic (neuro) endocrine mechanisms underlying the finely tuned regulation of the gonadotropic function underlying the estrous cycle can be altered in response to developmental exposure to BPA. Finally, this AOP approach allowed the experts of the ANSES's WG ED to conclude that BPA exhibits adverse effects on the estrous cycle that are related to endocrine MoAs which should justify the identification of BPA as an SVHC under REACH.



AOP, UNE APPROCHE ALTERNATIVE POUR L'EVALUATION DU RISQUE ?

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