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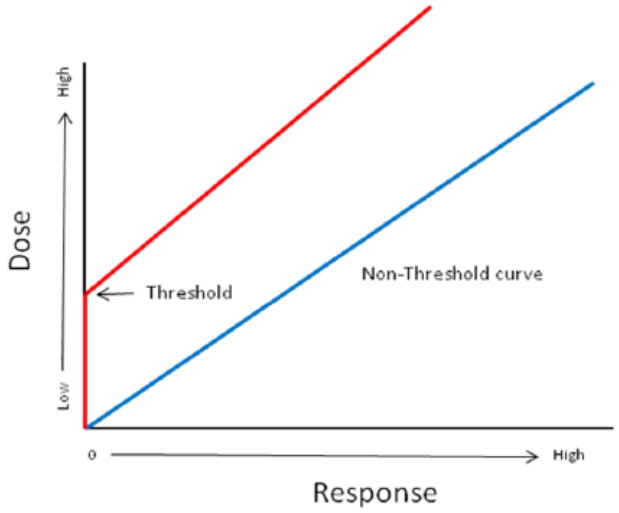
S T A T E M E N T of
Polish Association of Cosmetics and Home Care Products Producers
on
THRESHOLDS IN ENDOCRINE DISRUPTORS

A threshold is the exposure level or dose of an agent above which toxicity or adverse health effects can occur, and below which toxicity or adverse health effects are unlikely. This also includes doses or exposure below which homeostatic[1] changes are able to reverse any adverse effect.

Biological systems are capable of complex defense mechanisms in order to prevent toxic effects. Thresholds exist because, up to a certain point, the body can repair damage and detoxify chemicals to which it is exposed. Only if these mechanisms of repair are overcome, adverse effects are likely to occur. Therefore, a threshold for adverse effects can be established using state of the art testing methods in whole animals. The threshold can be low in certain development phases, but it can usually be determined with suitable methods. This concept is well accepted in toxicology and forms the basis for regulatory activities across all sectors and globally.

The next figure shows a comparison between substances where a threshold cannot be determine (blue curve) with substances presenting a threshold (red curve).



If a chemical presents a threshold, no toxicological effects occur until a certain dose is present in the body (red curve in the previous figure). However, if the substance does not present any threshold, any dose is sufficient to produce an adverse effect (blue curve in the figure). It must be noted that a non-threshold approach is used by risk assessors and regulators for certain forms of mutagenicity and genotoxic carcinogenicity, whilst a threshold approach is used for all other endpoints/effects. This non-

[1]Homeostasis is the property of a system that regulates its internal environment and tends to maintain a stable and relatively constant condition of properties. The properties constantly fluctuate within a certain range of values which are considered normal for the body. For example, body temperature or blood sugar levels fluctuate in order to respond and compensate external stimuli. Adverse effects occur when homeostatic mechanisms are not able to compensate and reverse these effects.

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threshold approach adopted for genotoxic carcinogens was developed at a time when modern insights into mechanisms of tumour initiation, promotion and progression and of physiological defence mechanisms were yet to be revealed. Currently, it is well known that the body presents different repair mechanisms that prevent, up to a certain concentration (or threshold), an adverse effect to occur. As such, biologically, the non-threshold approach does not seem consistent.

There is an ongoing discussion amongst the scientific community about the existence or not of thresholds and whether they can be safely determined. After years of debate, there is still no consensus on this topic. **Association believes that, in view of all the scientific evidence, EDs are chemicals where a safe threshold can be determined.**

We believe that safe levels can be defined for substances which are endocrine disruptors. A substance can only be called an endocrine disruptor if an adverse effect can be observed. Interference with the endocrine system is a mechanism of action and not an adverse effect itself. An adverse effect on the organ or tissue level clearly has a threshold which can be determined using accepted test methods. This is valid for acute, subchronic as well as long-term effects and also applies to effects on reproduction. These testing methods are designed to provide data to establish a NOAEL (No Observable Adverse Effect Level) and thus a threshold. Given the nature of the design of toxicological experiments where only a limited number of dose levels can be used, the true threshold is often significantly higher than the threshold determined in the tests.

The effect of an endocrine disrupting substance depends on how strongly the chemical binds to the respective hormone receptor. Hormones unfold their effects when they bind to a specific receptor. This binding process occurs according to the "lock-and-key principle". Many hormone active chemicals bind only weakly, because they do not fit perfectly into the receptor. Substances presenting a low affinity towards the receptor cannot compete with high affinity ligands (such as the natural hormones) unless their concentrations reach a sufficient level. This is why low affinity ligands or chemicals have no discernible effects at low concentrations.

A clear example of why EDs should be considered as chemicals where a threshold can be defined is the oral contraceptive pill. Contraceptive pills are designed to work as endocrine disruptors. Each pill contains a certain amount of hormones (normally a combination of estrogen and progestogen) and women need to take them daily in order to achieve the desired effect. If women don´t take the correct amount, or in other words, **if the dose is below the threshold**, the pill will not produce the effect to which it was designed. A minimum level of interaction between the chemical agent and the targets in the organism is required to produce a relevant effect.

Although EDs might act through sensitive windows of susceptibility, such as during fetal period, this is not sufficient to say that EDs do not present a threshold. Other chemicals that are not EDs can act during sensitive windows of development, such as developmental toxicants. Still, the risk posed by developmental toxicants is assessed by adopting a threshold approach. It is important to mention also that, although the foetus does not present a fully functional endocrine system, there are other homeostatic and repair mechanisms operating at the cellular level. Additionally, there are homeostatic mechanisms operating within the maternal organism that also counteract any initial perturbation induced by the chemical agent before it reaches the foetus. As such, the assessment of the risk posed by EDs should follow a similar route to other developmental toxicants with the definition of a safe threshold.

While special attention is required for particularly sensitive groups of the population (e.g. children or pregnant women) the safe use of chemicals can be supported by the correct use of safety factors during the risk assessment process. There is no scientific evidence that as a basic principle all endocrine disruptors have to be considered and assessed as substances where a threshold cannot be determined.