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Low Dose Effects:
Messages and Demands

- **On the thesis of low dose effects:**

  For some years, the scientific community has been giving much attention to the thesis of low dose effects. Data on this issue have been gathered and interpreted in numerous studies and research projects. Should this thesis be confirmed, the ensuing discussion of the consequences might necessitate profound changes in the chemicals assessment for certain substance groups. For example, test methods and assessment strategies would need to be adapted. However, to date there is no objective and scientific proof of this thesis.

- **Dose-effect relations / What is being discussed?**

  "Only the dose makes the poison" - this quote by the physician Paracelsus from the 15th century describes the fundamental rule of toxicology which applies to this day and means that the dose is decisive for the effect of a substance. It also follows that the effect of a substance gains in strength at increasing concentration and becomes weaker at lower concentration. For this reason, the dose-effect relationship is examined also in modern chemicals assessment. Concretely, a substance is tested at various concentrations according to generally recognized methods: inter alia, the dose or concentration at which no (adverse) effects are observed or expected, is determined. The technical term for this is "No Observed (Adverse) Effect Level" - NO(A)EL. The view prevails that substances in concentrations below the limit values, which are derived from the NO(A)EL, are safe.

- **How are low dose effects to be understood?**

  Currently, it is being discussed whether - contrary to the above-described principle - the adverse effect of a substance can increase at lower concentration, even far below the NO(A)EL value (so-called non-monotonic, U-shaped dose-effect relationship). Interpretations differ of the value at which one speaks of a "low dose". Up until now, there is no generally accepted definition. Some scientists assume that hormone active (endocrine) substances cause low dose effects, but proof of this substance property is lacking. Here, it needs to be taken into account that it is difficult at such low doses to distinguish between the really occurring effects and the inevitable background signals in the test methods.

- **Differentiation between observed effects and adverse effects**

  Every day we are exposed to many stimuli and substances. Quite naturally, the body responds to these influences, e.g. with a higher blood sugar level after food intake. The body can adapt itself and, for example, activate its metabolism. Normally, the body remains in balance irrespective of measurable reactions and effects. But there are also cases where stimuli or substances are harmful to the body. Therefore, it is important to differentiate between observed or measurable effects on the one side and harmful (adverse) effects on the other. Whilst the former are normal and even desirable, the latter need to be prevented.

- **State of science on low dose effects**

  Many research activities are controversially dealing with this issue, for example:

  - LRI-EMSG 56: Combined Low-dose Exposures to Anti-androgenic Substances
  - Vandenberg et. al. in Endocrine Reviews, June 2012, 33(3).
  - Rhomberg et. al. in Regulatory Toxicology and Pharmacology, June 2012.
  - ECETOC Report Technical Report 115 "Effects of Chemical Co-exposures at Doses Relevant for Human Safety Assessments"

The VCI's Demands

1. Use clear-cut definitions

For the discussion it is important to use generally agreed and clear-cut definitions. First of all, it needs to be defined how a "low dose effect" is to be understood.

In the VCI's opinion, "low dose" is the dose range clearly below the NO(A)EL value. Where adverse effects occur in this dose range, one should speak of low dose effects. By contrast, studies working with substance doses just below the NO(A)EL value provide no sound data in proof of the "low dose effect" thesis.

2. Consider only adverse effects in regulation

Chemicals regulation needs to be shaped in a way which regulates and prevents adverse effects. The goal is to derive safe limit values which preserve human health throughout a lifetime. For this purpose, it is not necessary to consider each and any effect in legislation. Especially with ever more sensitive measuring methods (transcriptomics, proteomics, metabolomics), scientific tests now enable observing even the slightest effects of substances - also where such small effects have no adverse impacts on health.

From today's viewpoint, it would be disproportionate to test in the chemicals assessment all theoretical questions with all conceivable methods in respect of low dose effects, because this would necessitate a very large number of additional animal studies and high costs - without providing any extra safety for consumers.

3. Weight-of-evidence approach

For a targeted discussion it is important to examine the thesis of low dose effects in a scientifically well-founded manner and based on generally agreed definitions - applying a clear weight-of-evidence approach which takes into account all existing studies. Morever, there is the fact that an above-average number of effect studies are published whereas studies which show no effect of a given substance are usually not published at all. The issue of low dose effects also involves the danger of normal biological processes observed in testing being misinterpreted as substance effects.

Irrespective of these problems, it is important to engage in an appropriate discussion based on all available data.

4. No regulation relying on a thesis

The "low dose effect" thesis could influence the entire chemicals assessment for the potentially concerned substance groups - with far-reaching practical and economic impacts. Therefore, it is essential from the VCI's position to have scientific proof of this thesis before even thinking about changes to the chemicals legislation.

Industry actively participates in ongoing research projects, in order to ensure the correct, appropriate and safe handling of its products. The strong commitment of the chemical industry reflects the major role of product safety in this industry's "Responsible Care" programme.