Principles, Benefits and Limitations of the NOEL Approach

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1 - Overview

The concept of the NOEL approach is, in itself, very simple. Many types of toxicology studies are performed utilizing a graded range of dose levels of test compound. The NOEL (No Observed Effect Level) is the highest dose level at which and below which no effects of the test compound are observed amongst the evaluated parameters. A refinement of this concept is the use of the NOAEL (No Observed Adverse Effect Level) which only takes into account effects which are regarded as adverse.

2 - Need for the NO(A)EL Approach

The NOEL (No Observed Effect Level) or NOAEL (No Observed Adverse Effect Level) is often the single statistic taken from a toxicology study, or series of studies, for use in risk assessment calculations. A toxicology package (normally including chronic rodent, non-rodent and teratology studies, etc...) is evaluated and the lowest NO(A)EL identified. The objective being to select the most sensitive species and test system to provide a conservative estimate of an exposure level which does not cause adverse effects, on which to base the risk assessment.

The NOEL value provides an estimate of the "safe" dose-level for the test species in the test system. In order to extrapolate to an estimate of the "safe" dose level in man (e.g. Acceptable Daily Intake, ADI, or Threshold Limit Value, TLV) the NOEL is divided by a Safety Factor (SF) or Uncertainty Factor (UF). Hence, the current need for the NOEL (or an equivalent) is based on its routine use in risk assessment.
3 - Definitions of Terms used in the NO(A)EL Approach and in Risk Assessment

The following terms are those most frequently encountered in publications encompassing the concept of the NO(A)EL.

- **NOEL** (no observed effect level) - An experimentally determined dose at which no statistically or biologically significant indication of toxic effects are observed.

- **NOAEL** (no observed adverse effect level) - An experimentally determined dose at which no statistically or biologically significant indication of the toxic effect of concern is observed.

- Adverse (effect) - Functional impairment or pathological lesion which may affect the performances of the organism or which reduces its ability to respond to additional challenge.

* See notes 1, 2, 3 and 4 which refer to principles and concepts relating to the NO(A)EL.

**Note 1**

The concept of a "dose-response" is generally accepted. "Empirical observations have generally revealed that as the dosage of a toxicant is increased, the toxic response (in terms of severity and/or incidence of effects also increases. This dose-response relationship is well-founded in the theory and practice of toxicology and pharmacology. Such behavior is observed in the following instances: in quantal responses, in which the proportion of responding individuals in a population increases with dose; in graded responses, in which the severity of the toxic response within an individual increases with dose; and in continuous responses, in which changes in a biological parameter (e.g., body or organ weight) vary with dose." Barns and Dourson (1988) [US EPA]

**Note 2**

Further, the concept of a "threshold" is also accepted. "In the case of [non-oncogenic] toxicity, organic homeostatic, compensating and adaptive mechanisms exist that must be overcome before a toxic endpoint is manifested. For example, there could be a large number of cells performing the same or similar function whose population must be significantly depleted before the effect is seen. The threshold concept is important in the regulatory context. The individual threshold hypothesis holds that a range of exposures from zero to some finite value can be tolerated by the organism with essentially no chance of expression of the toxic effect." Barns and Dourson (1988) [US EPA]