NOAEL approach vs BMD approach

In this guide

40. Both EFSA and the US EPA consider the BMD approach to be the more quantitative and scientifically advanced approach to deriving the RP compared to the NOAEL approach. In theory, the BMD approach uses all the available dose-response information within a given dataset. The NOAEL approach, in contrast, effectively uses only the data that make up the control group and one other dose group: the NOAEL/LOAEL group (EFSA, 2017; US EPA, 2012).

41. An important acknowledgment is that the NOAEL approach is ostensibly designed to identify a “no effect” level for a given substance. Slob and others have argued that the NOAEL should more accurately be understood as the dose at which no statistically significant effect is detected. As Slob notes in a 2014 publication: “a prominent misconception about the NOAEL approach is that the NOAEL reflects a dose without effects”. In reality, the “true” NOAEL could be lower than the statistically determined NOAEL. Slob notes that the NOAEL is not substantively different from a BMD in this regard: they both reflect a dose where the true effect is small. The primary difference is that, in case of a NOAEL, the effect size is not defined (but assumed to be small), while for a BMDL, the effect is predefined, so it is known that the size of the effect at the BMDL is not larger than this specified value (i.e. the Benchmark response, BMR) (Slob, 2014).

42. As the BMD approach does not calculate a “no effect dose” but rather is set at a predefined effect size, it has been suggested that additional uncertainty factors might be appropriate when using a BMDL as the RP. In their 2017 guidance, EFSA argue that this concern is based on the false assumption that a NOAEL is associated with the complete absence of adverse effect. Furthermore, based on the data from National Toxicology Program (US NTP) studies (Bokkers and Slob, 2007), EFSA concluded that the default values of the BMR are such that the BMDL, on average, coincides with the NOAEL. They concluded that additional uncertainty factors, beyond those normally applied are not necessary and HBGVs derived using a BMDL as the RP can be expected, on average, to be as protective as those derived from the NOAELs (EFSA, 2017).

43. The reliability of the NOAEL approach is also crucially dependent on the sensitivity of the test method. The likelihood of detecting a small effect is directly proportional to the sample size being studied. The larger the sample size at a given dose, the more power in statistical terms there is to detect such an effect. This also results in the effect that studies performed with fewer animals per group will tend to yield a higher NOAEL than equivalent studies performed with higher

numbers, due to decreased statistical sensitivity (EFSA, 2017). As noted by Haber et al., (2018) this is particularly undesirable in a regulatory context because it disincentivises better designed, larger studies in favour of smaller, less powerful ones.

44. The BMD approach also provides important information regarding the uncertainties in the data. The output of the BMD approach provides a quantitative assessment of data quality, as described by the confidence (or credible) intervals. In the NOAEL approach, experimental uncertainties resulting from, e.g. low study power or high variance, in the response effect are not captured (EFSA, 2022).

45. Another limitation of the NOAEL approach is the study design. As noted by Crump (1984), the NOAEL must necessarily be one of the study's experimental doses. This artificially constrains NOAEL assignment to arbitrary doses which often are a poor reflection of the data. The advantage of the BMD approach, is that the BMD can be any dose level, including a dose between the assigned study doses (Crump, 1984). This is partly a result of traditional study design protocols in toxicology. At a recent EFSA workshop, it was noted that the current OECD guidance on designing animal experiments take, by default, the goal to be detecting statistical effect levels. Therefore animal studies often limit the number of doses to maximise the statistical power at each dose group (EFSA Workshop, 2023). Slob notes that the BMD approach therefore, theoretically allows for more efficient use of animals. More information is obtained from the same number of animals, or conversely, similar information may be obtained from fewer animals, compared with the NOAEL approach (Slob, 2014).

46. As the dose-response output for the BMD models is linked to a predefined biological effect size (rather than threshold of statistical significance) comparisons across potencies of different substances, or of the same substances under different conditions, is possible. For this reason, EFSA note that the BMD approach is also suitable for the derivation of relative potency factors (RPFs) or toxic equivalency factors (TEF) for individual substances in a mixture that share a common mode of toxicological action (EFSA, 2017). For example, the BMD approach has been used to provide relative potency estimates for different organophosphates in toxicological studies (Bosgra et al., 2009).