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A consistent and transparent approach for calculation of Derived No-Effect Levels (DNELs) for petroleum substances

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ABSTRACT

The REACH legislation introduced Derived No-Effect Levels (DNELs) which are defined as 'the levels of exposure above which humans should not be exposed'. DNELs were required for several categories of petroleum substances and CONCAWE developed a consistent approach for their derivation. First, the No-Observed Effect Level from a relevant study was corrected for pattern and route of exposure to obtain a modified Point-of-Departure ($POD_{modified}$). Subsequently, the DNEL was calculated by dividing the $POD_{modified}$ by Assessment Factors (AFs) to adjust for inter- and intraspecies differences. If substance-specific information allowed, Informed Assessment Factors (IAFs), developed by CONCAWE were utilised. When little or no substance-specific information on those differences was known, default AFs from the guidance provided by ECHA were used. Some hazard endpoints did not lend themselves to calculation of DNELs (e.g. aspiration, dermal irritation, mutagenicity). DNEL calculation was considered not appropriate if adverse effects were not observed in tests conducted at a limit dose or if meaningful dose–response curves could not be developed. However, DNELs were calculated when hazards were identified, regardless of whether or not risk characterisation was required under REACH. Examples for gasoline, Lubricating Base Oils, gas oils and bitumen are provided to illustrate CONCAWE's approach.

1. Introduction

Legislation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) was accepted in the European Union in December 2006 (EC, 2006). This legislation, which entered into force in June 2007, applies to all chemicals manufactured in, or imported into the European Union in amounts greater than 1 ton/year. Petroleum substances, from a regulatory perspective, are considered to be chemicals and are subject to REACH legislation. Most petroleum substances are recognised by REACH as substances of "Unknown or Variable composition, Complex reaction products or Biological materials" ("UVCBs"). Assessing the intrinsic hazard

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; AD, Animal Dose; AF, Assessment Factor; BW, body weight; CLP, Classification, Labelling and Packaging Regulation; CNS, Central Nervous System; CSA, Chemical Safety Assessment; CSR, Chemical Safety Report; CONCAWE, the oil companies European organisation for environment, health and safety; DNEL, Derived No-Effect Level; DMEL, Derived Minimal-Effect Level; DSD, Dangerous Substances Directive; ECETOC, European Centre for Ecotoxicology and Toxicology Of Chemicals; ECHA, European Chemicals Agency; GI, gastro-intestinal; HED, Human Equivalent Dose; IAF, Informed Assessment Factor; IOELV, Indicative Occupational Exposure Limit Value; LBO, Lubricating Base Oil; LOAEC, Lowest Observed Adverse Effect Concentration; LOAEL, Lowest Observed Adverse Effect Level; MOA, Mode-Of-Action; OECD, Organisation for Economic Co-operation and Development; OEL, Occupational Exposure Limit; NOEC, No Observed Effect Concentration; NOAEC, No Observed Adverse Effect Concentration; NOAEL, No Observed Adverse Effect Level; PAC, Polycyclic Aromatic Compound; PBPK, Pharmacologically-Based PharmacoKinetic; POD, Point Of Departure; RCR, Risk Characterisation Ratio; REACH, Registration, Evaluation and Authorisation of Chemicals; SCOEL, Scientific Committee for Occupational Exposure Limits; SF, Scaling Factor; STEL, Short-Term Exposure Limit; TWA, Time-Weighted Average; UVCB, Unknown or Variable composition, Complex reaction products or Biological materials.

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properties and, where applicable, the risks associated with petroleum UVCBs can be challenging. Under its comprehensive Risk Assessment Programme on petroleum substances, the petroleum industry has developed methodologies that facilitate and improve the quality of such assessments. One of the methodologies employed was grouping of the individual petroleum substances into a distinct number of categories, based on their manufacturing processes (distillation, cracking, hydrotreatment etc.), physical/chemical similarities, likely composition (based on understanding of the manufacturing process) and tested or modelled environmental and human health hazard properties. Examples of such categories include low boiling point naphthas (gasolines), kerosines and bitumen (for a complete list of categories, see the Inventory of Petroleum Substances http://concawe.org/Content/Default.asp).

REACH requires a human health risk characterisation of substances classified according to the Dangerous Substances Directive as hazardous to human health. To this purpose, REACH introduced the concept of a Derived No-Effect Level (DNEL), which represents 'the level of exposure above which humans should not be exposed' (Annex 1, Chapter 1 "Human health hazard assessment", article 1.0.1 (EC, 2006)). DNELs play a crucial role in this process serving as benchmark value against which safe use can be determined in the risk characterisation process that compares measured or modelled exposure data for each of the identified uses and Exposure Scenarios of the substance against the DNEL. The outcome of this process may then prompt development of appropriate information on safe use (e.g. necessary risk management measures, supporting operational conditions). The ratio of exposure to DNEL yields a risk quotient, the Risk Characterisation Ratio (RCR), with values less than 1 indicating acceptable risk under REACH. This paper focuses on the derivation of the DNEL value.

The REACH legislation requires that appropriate DNEL values be calculated and documented in the Chemical Safety Assessment (CSA), to the extent that this is appropriate based on assessment of the available data, for any substance subject to registration which is manufactured or imported in quantities of 10 ton/year or higher. Since most petroleum substances are manufactured in quantities greater than this, the development of DNELs needed to be considered.

The legislation requires registrants to develop DNELs to address a broad range of potential health effects, the principal routes of exposure and exposed populations. As a consequence, the approach by which DNELs are to be developed is both extensive and complex. Guidance for preparing the CSA for a substance is available at the European Chemicals Agency (ECHA) website, (ECHA, 2008a); Chapter R.8 of this guidance is dedicated to the characterization of dose [concentration]–response for human health effects and the calculation of DNEL values. This first version of the guidance was developed by experts from Member States, NGO's and Industry and took into account existing guidance such as the documents developed by ICPS, ECETOC and EFSA (ECETOC, 2003; EFSA, 2005; IPCS, 2005). In general, there is limited experimental human data for petroleum substances. Hence DNELs are primarily based on results of experimental studies in rodent species, with the test substances being administered via a specified route (oral, dermal or inhalation).

Before calculation of a DNEL begins, one must first determine whether there is an actual need or requirement for such a value. If it is considered necessary, the first step in the calculation of a DNEL, is the identification of the exposed human population and of the relevant route and duration (acute, repeat dose etc.) of exposure. At this stage special consideration might be given to specific endpoints in relation to calculation of DNELs for petroleum substances, as discussed in a subsequent section of this paper. Assessment Factors for the subsequent calculations are then chosen to suit that particular combination of route and exposed population. Subsequently, a No Observed Adverse Effect Level (NOAEL) or a Lowest Observed Adverse Effect Level (LOAEL) is identified from the most relevant study for specific endpoints on biological or statistical grounds as the "Point Of Departure" (POD) for deriving a DNEL. If necessary, this POD is adjusted to provide a modified POD ($POD_{modified}$) by correcting for differences in exposure duration, exposure frequency, route of exposure, and/or level of activity, as compared to the human exposure situation for which the DNEL is derived. Finally, the DNEL for the specified endpoint and route of exposure is calculated by dividing the $POD_{modified}$ by a series of Assessment Factors (AFs). These AFs are numerical values that take into account the variability and uncertainty inherent in the extrapolation of experimental data, particularly between and within species (intra- and interspecies differences), as well as data limitations. The ECHA Guidance in chapter R.8 provides recommendations on AFs to be used in this process. It should be borne in mind that if the POD is not based on substance-specific data but has been obtained in other ways, such as read-across, as explained in Annex XI of the REACH legislation (Section 1.5: grouping of substances and read-across approach) expert judgment is needed to determine whether additional AFs may be required.

It is important to recognise that, in principle, AFs can be either specific values for a substance or category of substances, or they can be more generic values. In the latter case, the value is often referred to as a 'default' factor. For example, the AFs provided in the ECHA guidance documents are considered to be 'default' factors, applicable to substances for which data are lacking or for which very little or no specific information about inter- and intraspecies variation in response is available (ECHA, 2010). When specific data exist for a substance or category of substances and these provide more precise information, the substance-specific data can be used to establish specific AFs that apply only to the substance or category of substances to which the data relate. As noted in ECHA's Guidance, "Preferably, the value for each individual Assessment Factor is based on substance-specific information. However, although sound in principle, in practice the approach has limitations (data are often scarce, especially toxicodynamic data, and human data) and, therefore, default AFs often need to be used. Each step in the process, including any choice for an AF value, whether substance-specific or default should be explained as transparently as possible, with a qualitative narrative in the Chemical Safety Report (CSR)." Furthermore, ECHA notes that "Although very often necessary to rely upon, the default AFs represent a fall-back position rather than the starting point." The modified AFs based on substance-specific information derived by CONCAWE (the oil companies' European organization for environment, health and safety) are referred to here as Informed Assessment Factors (IAFs).

A number of toxicological endpoints of relevance to petroleum substances have been well investigated and the mechanisms of action underlying the observed toxicity are understood. An understanding of the Mode-Of-Action (MOA), in combination with an understanding of the chemical classes of molecules present in the various petroleum substances, supports the development of IAFs that can be used to derive DNELs for petroleum substances. The following information was used by CONCAWE during development of IAFs and DNELs for petroleum substances:

1. guidance provided by ECHA as the core building block,
2. guidance developed by ECETOC on derivation of IAFs for human health risk, assessment (ECETOC, 2003, 2010), and,
3. most importantly, assessment of the relatively large database of toxicological, studies and other available health information on petroleum substances.

Given this background, the main objective of the following sections of this paper is to describe a consistent and transparent