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Haber's rule duration adjustments should not be used systematically for risk assessment in public health decision-making

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ABSTRACT

Human health risk assessment can be used to support decisions for public health regulations and actions. Characterizing the hazards of inhaled toxicants generally includes extrapolation from observations on experimental animals, subjected to intermittent or subchronic exposures, to a human environmental context with exposure that is usually continuous and long-term. The extrapolation is usually based on a simple linear relationship derived from Haber's rule which assumes that, for a given chemical compound, multiplying the same concentration by the same duration of exposure will yield the same biological response. This study assessed the reliability of this assumption. The p-power in the equation $C \times t^p = k$ was calculated for 21 chemicals, based on a comparison of LOAELs for subacute, subchronic and chronic durations. A bibliographic survey was then carried out to study the reliability of the intermittent-to-continuous exposure adjustment factors currently used in risk assessment. The results showed that the value of p, assumed to be 1 in risk assessment methodology, was not in fact equal to 1 for any of the selected chemicals. Moreover, in the case of respiratory tract irritation, the value of p varied from 0 to 0.44, as confirmed by experimental studies. These results suggest that a more in-depth and case-by-case approach is required for regulatory toxicology, based on toxicokinetics and toxicodynamic data analysis for each toxicant before applying a temporal-adjustment factor.

1. Introduction

In 1983, a framework for human health risk assessment was described by the US National Research Council in a report known as the "Red Book" (NRC, 1983). It involves the qualitative and quantitative characterization of the potential health effects of chemicals on humans and ecosystems. This approach is now widely used by government agencies and authorities in Europe for making policy decisions. It includes the following steps: hazard identification and dose–response assessment (hazard characterization), exposure assessment and risk characterization. In the hazard characterization step, the identification of the target organs, dose–effect relationships and critical effects generally includes extrapolation of data from controlled animal-based experiments to a human environmental context. This is related to the difficulty of using epidemiological data to derive human toxicity reference values (TRVs) such as RfC, MRL or REL[1] for non-cancer risk assessment. These values are generally based on the following steps: the choice of a critical effect by examining data in experimental animal species that are relevant to humans, the choice of a critical study of good quality which shows a dose–response relationship, the identifica-

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; BMD, benchmark dose; BMDL, benchmark dose level; Cs, subchronic critical dose; Cc, chronic critical dose; Ts, subchronic duration of exposure; Tc, chronic duration of exposure; LOAEL, lowest observed adverse effect level; MRL, minimal risk level; NOAEL, no observed adverse effect level; OEHHA, Office of Environmental Health Hazard Assessment; REL, reference exposure level; RfC, reference dose; RIVM, Dutch Institute for Public Health and the Environment; TRV, toxicity reference value; UF, uncertainty factor; US-EPA, US-Environmental Protection Agency; WHO, World Health Organization.

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[1] The RfC is the reference dose derived by the US EPA (U.S. Environmental Protection Agency), the MRL is the minimal risk level derived by ATSDR (Agency for Toxic Substances and Disease Registry) and the REL is the reference exposure level derived by the Office of Environmental Health Hazard Assessment from the California EPA (OEHHA). In this paper, all these values are grouped together under the term "toxicity reference values" (TRVs) defined as the estimated exposure to the human population, including subgroups at risk, that is likely to be without appreciable risk of harmful effects in specified exposure conditions (time, route).

tion of a critical dose ("the point of departure") which may be a no observed adverse effect level (NOAEL), a lowest observed adverse effect level (LOAEL) or a statistically derived value corresponding to a specified level of response (benchmark dose (BMD)), the application of uncertainty factors (UFs) to take into account the variability and the uncertainty due to experimental conditions and human exposures. These uncertainty factors take account of differences between animals and humans (interspecies variability (UF_A)), differences between average human and sensitive subgroups included in the general population (intraspecies variability (UF_H)), the use of a LOAEL or a BMDL (benchmark dose level – the lower 95% confidence limit of the benchmark dose) rather than a NOAEL (the LOAEL uncertainty factor (UF_L)) and the lack of chronic toxicity studies (subchronic uncertainty factor (UF_S)) (Chou et al., 1998; US EPA, 1994, 2002; Pohl et al., 2010).

One of the current challenges in regulatory toxicology is the extrapolation of data obtained from a specific protocol to the general population. In addition to the use of uncertainty factors, interspecies adjustments based on allometric scaling or respiratory dosimetry (according to the route of exposure, i.e. oral or inhalation) can be applied directly to adjust the critical dose so as to give a human equivalent dose. Moreover, duration adjustments could be used in the case of inhalation TRVs to take account of the differences in frequency and duration of exposure between animal experiments or occupational studies and the general population (i.e. intermittent versus continuous exposure). Adjustment of duration to continuous lifetime exposure is currently applied as a default assumption to derive inhalation non-cancer TRVs in risk assessment: for example, in laboratory assays, rodents are usually exposed for several hours a day, 5 days a week for several months whereas workers are exposed for 8 h a day for 5 days a week. This duration adjustment factor is calculated using a simple linear relationship derived from Haber's rule assuming that, for a given chemical compound, the same calculated values of the concentration of exposure multiplied by the duration of exposure will yield the same biological response, i.e. $C \times t = k$ (US EPA, 1994; Chou et al., 1998). In other words, the basic assumption in applying this duration adjustment is the applicability of the concept of a cumulative dose. For example, in an inhalation study in which rodents are exposed to 10 ppm for 6 h a day, 5 days a week, the adjusted dose would be 1.8 ppm ($10 \times 6/24 \times 5/7$).

This default assumption is usually applied as a conservative approach by risk assessment agencies such as the ATSDR, the US EPA in the United States, or ANSES in France, even if this will generally result in an overestimated risk. In France, human TRVs from these agencies are used: (i) to recommend regulatory health-based guidelines (in water, in air, etc.), (ii) to carry out a preliminary health risk assessment in a regulatory context, before authorizing an industrial plant or requiring risk reduction strategies and (iii) to carry out a risk assessment for a given population group exposed to chemicals in order to take public health measures (monitoring, screening, etc.). In this last case, default TRVs should be used with caution when interpreting the results of a health risk assessment because an overestimated risk may lead to unjustified concern and disproportionate measures. This study was carried out to evaluate the reliability of the duration adjustment hypotheses that are applied for deriving TRVs in a public health context. Only non-cancer TRVs are considered for inhalation exposures.

2. History of Haber's rule and its use in health risk assessment

In the early 1900s, several scientists analyzed the quantitative correlation between the concentration of a chemical and the duration of exposure (Warren, 1900; Flury, 1921; Haber et al., 1924). Their research led to the definition of a correlation between the acute exposure to poison gases (mustard gas, chlorine, hydrogen cyanide) and the time before death in cats based on the following equation: $C \times t = k$ which became known as "*Haber's rule*". However, this rule, which was demonstrated in a very specific context (poison gases, acute exposure and time before death in cats), may be considered as a specific, simple case of the more general formula $C^{\alpha} \times t^{\beta} = k$, where $\alpha = \beta = 1$ (Miller et al., 2000). Although this simple rule was only verified for acute exposure and further observed in particular cases such as cumulative or carcinogenic chemicals (Miller et al., 2000; Gaylor, 2000; Remillard and Bunce, 2002), most risk assessment authorities have used this duration adjustment as a default factor based on the recommendations of the US EPA for chronic exposures (US EPA, 1994). Because this duration adjustment generally results in a lower critical dose than the unadjusted dose, risk assessors consider that it provides an additional margin of safety for public health. For the acute RELs from OEHHA, the limitations of the equation $C \times t = k$ were recognized and the formula $C^n \times t = k$ was used, with "n" being determined empirically (OEHHA, 1999a,b). The value of "n" is based on the article from Ten Berge et al. (1986), according to which, for a certain number of substances, "n" varies between 0.8 and 3.5 for acute effects. Three equations are commonly used in the literature to represent Haber's law, $C^a \times t^b = K$ or $C^n \times t = K$ or $C \times t^p = K$ the most general being the first. If a and b are different from zero, these three equations are equivalent. If $a = n = 0$, the observed effect is only dependant on the duration of exposure. If $b = p = 0$, the observed adverse effect does not depend on the exposure duration but only on the concentration.

The OEHHA recommends using the formula $C^n \times t = k$ for duration adjustment when the duration of exposure studied differs from that for which the acute REL was calculated (OEHHA, 1999a,b).

The concept of Haber's rule is also applied in risk assessment when extrapolating the effects induced by subchronic exposure to chronic exposure (Kramer et al., 1996; Malkiewicz et al., 2009). For example, a subchronic uncertainty factor (UF_S) is applied by the US EPA to adjust the duration of exposure when a subchronic study is used to derive a chronic RfC (US EPA, 1994). The default approach is to use a value of 10, assuming that a high dose of a compound received over a short period of time is equivalent to the corresponding low dose spread over time (US EPA, 2002; Stedeford et al., 2007). In practice, a UF_S was applied to 35% of the RfCs in the IRIS database. Of the 32 RfCs defined using a UF_S, a factor of 3 was applied in 12 cases and a factor of 10 in 20 cases. Moreover, for 9 of the 12 RfCs with a UF_S of 3, Haber's rule was explicitly stated to be not applicable. For example, when defining the RfC for 1,2-dichloropropane based on respiratory effects (hyperplasia of the nasal mucous membrane), the US EPA applied a UF_S of 3. This value was justified by the fact that the critical effect increases little with time and duration adjustment is not applicable in this case (consultation www.epa.gov/iris in March, 2008). Nowadays, government agencies, in particular the US EPA, encourage assessors to look for specific data on a case-by-case basis in a scientific manner when sufficient information is available (US EPA, 2002). It appears important to take better account of the physical and chemical characteristics and the way in which the compounds act. The default assumption should only be used in the case of inadequate data.

3. Materials and methods

This study used two approaches for assessing the reliability of duration adjustments based on the concept of Haber's rule in regulatory toxicology, one by comparing subacute, subchronic or chronic data, and the other considering a mechanistic toxicological approach using several case studies with different exposure scenarios related to frequency or duration resulting in the same $C \times t$ product.