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Incorporation of dosimetry in the derivation of reference concentrations for ambient or workplace air: A conceptual approach

Adriana R. Oller [a,*], Günter Oberdörster [b]

[a] NiPERA, 2525 Meridian Parkway, Suite 240, Durham, NC 27713, USA
[b] University of Rochester, Department of Environmental Medicine, 575 Elmwood Avenue, Medical Center Box 850, Rochester, NY 14642, USA

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ABSTRACT

Dosimetric models are essential tools to refine inhalation risk assessments based on local respiratory effects. Dosimetric adjustments to account for differences in aerosol particle size and respiratory tract deposition and/or clearance among rodents, workers, and the general public can be applied to experimentally- and epidemiologically-determined points of departure (PODs) to calculate size-selected (e.g., PM_{10}, inhalable aerosol fraction, respirable aerosol fraction) equivalent concentrations (e.g., HEC or human equivalent concentration; REC or rodent equivalent concentration). A modified POD (e.g., HEC) can then feed into existing frameworks for the derivation of occupational or ambient air concentration limits or reference concentrations. HECs that are expressed in terms of aerosol particle sizes experienced by humans but are derived from animal studies allow proper comparison of exposure levels and associated health effects in animals and humans. This can inform differences in responsiveness between animals and humans, based on the same deposited or retained doses and can also allow the use of both data sources in an integrated weight of evidence approach for hazard and risk assessment purposes. Whenever possible, default values should be replaced by substance-specific and target population-specific parameters. Assumptions and sources of uncertainty need to be clearly reported.

1. Introduction

The derivation of concentration limits or reference concentrations for airborne particulates begins with the identification of a point of departure (POD) based on health effects observed in animal or human studies (i.e., original study populations). Examples of PODs are no adverse effect concentration (NOAEC), low adverse effect concentration (LOAEC), and $BMCL_{10}$ (the 95% lower confidence limit concentration associated with a 10% response). The initial PODs are usually modified to consider differences in exposure duration between the original study participants (animal or human) and the desired target population (workers, general public, etc.). Finally, assessment factors (e.g., extrapolation factors, uncertainty factors, safety factors) are applied to the modified PODs and the final concentration limits or reference concentration are derived.

* Corresponding author.

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Nomenclature

$BMCL_{10}$	lower 95th percent confidence limit on the concentration resulting in a 10% response
CAPs	concentrated ambient particles
DNEL	derived no effect level
ECHA	European Chemicals Agency
GBS	granular biopersistent particles without any specific toxicity
GSD	geometric standard deviation
HEC	human equivalent concentration
EC	equivalent concentration
LOAEC	low observed adverse-effect concentration
MAK	Maximale Arbeitsplatz-Konzentration
MMAD	mass median aerodynamic diameter
MPPD	multiple-path particle dosimetry model
NOAEC	no-observed adverse-effect concentration
OEL	occupational exposure limit
PEL	permissible exposure limit
PM	particulate matter–ambient air
PM_{10}	size-selected aerosol fractions, $< 10\ \mu m$
$PM_{2.5}$	size-selected aerosol fractions, $< 2.5\ \mu m$
POD	point of departure
PSD	particle size distribution
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical Substances (European Union)
REC	rodent equivalent concentration
RfC	reference concentration
SA	surface area

For the inhalation route of exposure, the particle size distribution (PSD) of the aerosols and the breathing parameters affect the overall deposition of particles (i.e., deposited dose) in the various regions of the respiratory tract (i.e., extrathoracic, tracheobronchial, alveolar). Furthermore, it is recognized that it is the deposited or retained dose in a given respiratory tract region that is associated with adverse health outcomes (either local effects or systemic effects). For example, lung inflammation and lung fibrosis are expected to be associated with the retained doses in the alveolar region of the respiratory tract; while the retained doses in the extrathoracic region may be more relevant for nasal tumors (e.g., Nieboer, Thomassen, Chashchin, & Odland, 2005).

Yet, consideration of equivalent doses between original and target populations with respect to differences in airborne particle size distribution has not always been part of inhalation risk assessment frameworks. For example, in the U.S., the Environmental Protection Agency (EPA) has considered equivalent respiratory tract doses in the derivation of ambient air reference concentrations (RfC) based on animal studies since 1994 (U.S. EPA, 1994). The U.S. Occupational Safety and Health Administration (OSHA), by contrast has not; while the National Institute for Occupational Safety and Health (NIOSH) has only recently began to consider dosimetric models in their permissible exposure limit (PEL) derivations (e.g., NIOSH (2011) PEL derivation for titanium dioxide, NIOSH (2013) PEL derivation for carbon nanotubes). In the European Union, Germany's MAK Commission considered dosimetric differences between rodents and humans for the first time when deriving workplace exposure limits for granular biopersistent particles without any specific toxicity (GBS) (MAK, 2012). By contrast, EU REACH guidance on the derivation of derived no effect levels (DNELs) only takes differences in breathing conditions into consideration but not differences in deposited or retained doses (ECHA, 2008). Furthermore, no regulatory framework to date envisions the use of one PSD for the original (e.g., rodent) population and a different PSD for the target (e.g., human) population.

Figure 1 illustrates a general conceptual approach to derive long term air reference concentrations based on chronic respiratory effects after inhalation. In this approach, the starting POD could be derived from either animal studies (solid arrows) or workers' studies (open arrows). Deposited doses are calculated using the PSD for each original population's aerosol, while the deposited doses in the target populations considers the PSD of the target population's aerosol. Under the assumption that equivalent retained doses in animals and humans will be associated with the same type and extent of a response, a human equivalent concentration in workers (HEC-W) corresponding to an experimental rat aerosol concentration (e.g., NOAEC or LOAEC) can be calculated using the workplace PSD as input to the dosimetric model (Fig. 1, middle solid arrows). Similarly, the HEC for the general public (HEC-P) can be calculated based on the rat PSD when the ambient air PSD is used as input to the dosimetric model (Fig. 1, right solid arrows). Finally, it is also possible to derive an equivalent concentration for the general public (EC-P) based on the ambient air PSD and on a POD identified in workers' studies (Fig. 1, open arrows). In this case dosimetric models can be used to calculate equivalent concentrations using the PSD of the workplace for workers and the PSD of ambient air for the general public.

It is understood that once the modified PODs are calculated (as HEC-W, HEC-P or EC-P), assessment factors specific for each combination of original and target populations, as well as for the measured health endpoints will be applied as described in each particular risk assessment framework. These assessment factors will cover those sources of uncertainty or variability that have not already been incorporated into the dosimetric adjustment (e.g., differences in exposure duration, susceptibility, etc.).

While Fig. 1 describes the calculation of HECs (human target population) from an original rodent study, it is also appropriate to reverse the process. Human exposure data (e.g., from an epidemiological study) with information on PSD of workplace aerosols can be used to predict rodent equivalent concentrations (RECs) that can be used in an experimental PSD aerosol. This would be helpful for designing rodent studies to identify mechanisms of toxicity or to generate dose–response data on health effects (PM-associated effects) identified based on epidemiological studies (Brown, Wilson, & Grant, 2005).