Published in final edited form as:

J Aerosol Sci. 2016 September ; 99: 40–45. doi:10.1016/j.jaerosci.2016.01.015.

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

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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., PM₁₀, 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.

Keywords

MPPD model; human equivalent concentration; risk assessment; point of departure

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

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Adverse Effect Concentration (NOAEC), Low Adverse Effect Concentration (LOAEC), and BMCL₁₀ (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.

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 et al., 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 begun to consider dosimetric models in their PEL (Permissible Exposure Limit) derivations (e.g., 2011 PEL derivation for titanium dioxide, 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 (Figure 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 (Figure 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 (Figure 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 Figure 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 et al., 2005). Furthermore, REC calculations based on human data could help design animal studies for testing medical treatments for respiratory conditions associated with inhalation exposures (e.g., potential application of nanoparticles as carriers for medications).

In this paper we describe a conceptual approach for incorporating dosimetry into the risk assessment for the inhalation route of exposure and local respiratory tract effects (Figure 1). In the following sections we critically discuss some of the main issues that need to be considered when applying this approach.

2. Dosimetric Models and Dose Metrics

Rodents and humans have physiological and anatomical differences in their respiratory tract (e.g., respiratory tract structure, surface area, number of alveoli, breathing parameters). These differences result in differences in particle deposition, deposited doses, and retained doses in the various regions of the respiratory tract, for different PSDs. For example, most of the inorganic aerosols tested for carcinogenicity in the National Toxicology Program (NTP) rodent inhalation studies have a Mass Median Aerodynamic Diameter (MMAD) around 2 μm , and Geometric Standard Deviation (GSD) of approximately 2. These experimental aerosols likely have different PSD, inhalability and respirability from those to which humans are exposed in occupational environments (e.g., inhalable, thoracic or respirable PSD aerosol fractions) or in ambient air (e.g., $\text{PM}_{2.5}$ or PM_{10} size-selected aerosol fractions). Figure 2 provides an example of the differences in deposited doses (normalized by epithelial surface area) in the three regions of the respiratory tract for rats and humans exposed to the same concentration and PSD of different particle size aerosols of the same substance. Figure 2 is based on data presented in Oller et al. (2014).

Differences in breathing parameters also exist between rats and humans, between genders, and between workers and the general public, including children and adults, healthy and infirmed. Therefore, to compare respiratory effects between rodents and humans or between workers and the general public, it is not appropriate to just compare exposure levels but rather we need to consider the most relevant doses for the affected regions of the respiratory tract (e.g., deposited doses if effects are acute or clearance rates are similar; retained doses if effects are chronic or clearance rates differ between original and target populations).

Models such as the Multiple Path Particle Deposition (MPPD) model allow us to predict deposited doses in the various regions of the respiratory tract of rodents and humans using species-specific anatomical and physiological parameters and information on the characteristics of the aerosols (e.g., MMAD, GSD, effective aerosol density) (e.g., Anjivel and Asgharian, 1995; Asgharian et al., 1999; Asgharian and Price, 2009; Asgharian et al., 2014).

To compare doses between original and target populations the dose-metric that more closely relates to the observed toxicity effects needs to be selected. In the selection of dose metrics, the mode of action for toxicity and the dissolution rate of the particles should be considered. Possible options include: particle mass, particle number, particle surface area, and particle reactivity. For particles with high dissolution rates in the lung, steady state level is reached quickly, and the daily deposited and the long term retained doses may be similar. For these particles, mass may be a more appropriate metric while for poorly soluble particles other metrics should be considered to characterize the deposited or retained dose (e.g., surface area or surface reactivity). Further discussion on dose-metrics can be found for example in Brown et al. (2005) and Morfeld et al. (2015).

When extrapolating exposures from rodents to human, the absolute deposited doses for a given concentration, duration of exposure, PSD and other aerosol characteristics, are greater in humans than rodents due to differences in the size of the respiratory tracts and the greater inhaled air volume. Thus, various normalization parameters must be considered: lung weight, tracheobronchial or alveolar surface area, number of alveolar macrophages or epithelial cells, number of alveoli, *etc.* (Jarabek et al., 2005). For poorly soluble particles that deposit and clear along the surface of the respiratory tract, the particle mass or particle surface area per epithelial cell surface area are often considered appropriate dose metrics to correlate with an inflammatory response (Jarabek, 1995; Oller and Oberdörster, 2010; Oller et al., 2014). For fibrosis, the retained doses per gram of lung may be more relevant (Oberdörster, 1989). When comparing different human populations, information on gender and height can be used to predict differences in lung volume (e.g., Park et al., 2015). For further guidance and discussion about normalizing parameters please see Brown et al. (2005); Jarabek et al. (2005); U. S. EPA (2004); Oberdörster (1996).

3. Particle Clearance and Retained Doses

Differences in particle clearance between rodents and humans affect the long-term retained doses. Both the *in vivo* dissolution rate of particles as well as the respiratory tract regions need to be considered since the predominant clearance mechanisms differ from region to

region, and also for low versus high retained doses (Brown et al., 2005). In general, clearance rates for readily soluble particles that are removed mainly by dissolution are not expected to differ between rats and humans. For poorly soluble particles at non toxic, no overload levels, mechanical clearance via macrophages is expected to differ by up to 10-fold between rats and humans (e.g., retention half-times of approximately 50-to-80 days in rats and 250-to-700 days in humans under non impaired clearance conditions) (e.g., Bellmann et al., 1991; Gregoratto et al., 2010; Pauluhn, 2009; Borm et al., 2015). Steady state of retained doses is achieved after several months in rats but it takes about 4 to 10 years in humans (i.e., about 5 retention half-times). When data on retention half-times are lacking but data on build-up of lung burdens during repeat exposure (e.g. subchronic or chronic rodent studies) are available, it is possible to use the MPPD model to estimate daily deposited doses and calculate particle clearance rates and retention half-times in rats or mice (e.g., Oller et al., 2014). For newly designed rodent studies It would be important to measure lung burdens and include a sufficiently long post exposure recovery time to determine retention half-times (Pauluhn, 2009; 2014).

4. Aerosol Properties

The effective density of the aerosol particles, which differs for each substance and even for different compounds of the same substance (e.g., a metal) or for agglomerated versus non agglomerated forms of the substance, will affect deposition. When calculating a reference concentration based on data from animal studies with pure substances, the density of that substance will be the same as the effective density, as long as the aerosol does not consist of agglomerates. The substance's density can then be used as input for the MPPD model. For agglomerates or aggregates, the effective aerosol density has to be determined; packing density could be used as surrogate for this when other information is not available. However, when the starting study is an epidemiological study, exposure to particulates is seldom to a single or pure substance. Rather, particles can have mixtures of compounds that include the substance under study. In this case it would be more precise to measure the effective density of these workplace aerosols from calculations of mass and volume of material collected on stages of cascade impactors (Miller et al., 2013). This density can be used as input to the MPPD model to estimate the deposited or retained doses in exposed workers that may be associated with the presence or absence of an adverse effect.

To assess PSD (MMAD, GSD) of workplace and environmental aerosols several sampling devices exist. Cascade impactors represent the largest family of aerosol spectrometers commercially available (Vincent, 2007). In these devices, the sampled aerosol passes through a succession of stages, at each of which the aerosol-containing jet is directed through a series of nozzles with decreasing diameters onto a solid surface. Particle deposition takes place by impaction. The distribution of the collected particulate matter on the successive stages – including the backup filter - provides a means for assessing the particle size distribution in terms of aerodynamic diameter of the aerosol. However, cascade impactors differ in the range of particle sizes that they collect, while the PSD of workplace aerosols can range widely from large (>100 µm) to nanosize particles < 100 nm). Conventional cascade impactors have upper size limits of approximately 20 µm, although the inlets can be modified for the collection of the inhalable fraction (e.g., the modified

Marple and the modified Andersen cascade impactors allow collection of personal measurements up to 100 μm in aerodynamic diameter; Kerr et al., 2001; Wu and Vincent, 2007; Vincent et al., 2001). The Sioutas personal cascade impactor (Misra et al., 2002) is most appropriate for sampling aerosols with aerodynamic diameters below 10 μm . For nanosize aerosols, samplers like the nanoMOUDI (Micro-Orifice Uniform Deposition impactor) with a lower cut-size limit of 10 nm can be selected (Vincent, 2007).

5. Discussion

Dosimetric models such as the MPPD model have been gaining in scope, refinement and acceptance over recent years and they can play an essential role in risk assessment. These models can help fill in a void in the extrapolation of effects from rats to humans and in the comparison of animal and human data for the same effects of interest. When both human and animal datasets are available for similar health endpoints (e.g., lung fibrosis for which histopathology results may be available from rats and lung function tests or X-ray opacities may be available from humans), comparisons of responses at equivalent exposure levels can inform toxicodynamic differences between the two species. Brown et al., (2005) used the MPPD model to compare lung doses predicted to occur in humans and in rats exposed to Concentrated Ambient Particles (CAPs) and make inferences about the responsiveness of these species to the effects of CAPs. Oller et al. (2014) used the MPPD model to compare fibrotic responses in rats and humans at equivalent concentrations of a soluble nickel compound as a means to inform toxicodynamic differences in response between these two species.

The MPPD model can also be used to assess the influence that parameters such as age, exercise, and diseased state can have on deposited and retained doses in the human population and to assess the influence that the characteristics of the aerosols (MMAD, GSD, solubility, density, hygroscopicity) can have on these doses. These types of analyses can help inform the selection of assessment factors that are applied to account for intra-human variability in response and uncertainties in the risk assessment. Dosimetric models can also identify the most influential parameters that could be targeted for further research to obtain more robust information.

The strength of the obtained results will be predicated on the quality of the model input data. Robust characterization of experimental, ambient air or workplace exposures using cascade impactor type of samplers as well as information on environmental or workplace aerosol particle density are needed, depending on the objective. As much as possible, substance - specific (e.g., agglomeration state) and species-specific (e.g., breathing parameters) data should be collected. Importantly, all of the assumptions and input parameters need to be reported in detail so that uncertainties in the estimates of modified PODs using the MPPD model can be clearly understood and reflected in the overall risk assessment results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This work was in part supported by NIEHS grant P30 ES01247 (G. Oberdörster).

Biography

Günter Oberdörster, DVM, Ph.D., is Professor Emeritus in the Department of Environmental Medicine (University of Rochester). His research includes the effects and underlying mechanisms of lung injury induced by inhaled non-fibrous and fibrous particles, including extrapolation modeling and risk assessment. His influential studies with ultrafine particles have raised awareness about the unique biokinetics and toxicological potential of nano-sized particles. He earned his D.V.M. and Ph.D. (Pharmacology) from the University of Giessen in Germany. Günter has served on many national and international committees and has received several scientific awards. He is on the editorial boards of several scientific journals and Associate Editor of *Environmental Health Perspectives*.

Adriana Oller, Ph.D., D.A.B.T, obtained a Master's degree in Biochemistry from Buenos Aires University (Argentina) and a Ph.D. in Genetic Toxicology at the Massachusetts Institute of Technology (Cambridge, MA), for research on spontaneous mutations. She continued genetic toxicology research at the Lineberger Cancer Research Center and at NIEHS in North Carolina. In 1994, she joined the staff of the Nickel Producer Environmental Research Association (NiPERA, Inc.). During the last 20 years Adriana helped manage the human health research program for NiPERA, Adriana has authored more than two dozen peer-reviewed publications, participated in expert panels and served in JEM's editorial board from 2004 until 2006.

Nomenclature (as table)

BMCL₁₀	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
PM10	Size-selected aerosol fractions, < 10 µm)
PM2.5	Size-selected aerosol fractions, < 2.5 µm)
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

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Highlights

- Dosimetric models are essential tools for inhalation risk assessment
- Characterization of deposited or retained doses is key for dosimetric extrapolation
- Regulatory bodies could use different aerosol sizes for original and target populations
- Comparison of animal and human equivalent exposures can inform species' response

Figure 1.

Concept for the incorporation of dosimetry to calculate equivalent concentrations (HEC-W, HEC-P, EC-P). These equivalent concentrations are the modified PODs that can be used to derive occupational or ambient air reference concentrations after application of appropriate assessment factors (AF-W, AF-P). [R: Rat; W: Worker; P: Public; AF: Assessment Factor; HEC: Human Equivalent Concentration; EC: Equivalent Concentration; NOAEC: No Observed Adverse Effect Concentration].

Figure 2.

Comparison of respiratory tract deposited doses per surface area (ng/cm²) in rats and humans breathing aerosols with the same concentration and PSD for 1 hour. Note the log scale for the Y-axis. Experimental aerosol PSD ($MMAD = 2.21 \mu m$; $GSD = 1.97$); workplace inhalable aerosol PSD ($MMAD = 61.2 \mu m$, $GSD = 3.52$); ambient air 3-modal PSD (Aitken mode, 16% mass, $MMAD = 0.07 \mu m$, $GSD = 1.7$; accumulation mode, 50% mass, $MMAD = 0.329 \mu m$, $GSD = 1.8$; coarse mode, 34% mass, $MMAD = 4.71 \mu m$, $GSD = 2.5$). ET: extrathoracic; TB: tracheobronchial; AL: alveolar. Example based on data presented in Oller et al. (2014). MMPD model version 2.11. Epithelial surface area values based on data from Miller et al. (2011).