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Issues of dosimetry in inhalation toxicity

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Abstract

A major issue of inhalation toxicity is that of dose. An inhaled dose is more difficult to determine than the dose from other routes of administration. Via oral or parenteral routes, a discrete amount of test substance is given in a bolus. In inhalation toxicology, the delivered dose depends on the exposure concentration and duration, particle size, and associated changes in breathing patterns. Over the past few decades, the concept of dose as applied to toxicological studies has changed considerably. Initially, 'dose' simply meant the concentration in the atmosphere in inhalation studies (or the amount ingested or instilled into the gastrointestinal tract in oral dosing studies) times the duration of study. The extrapolation from one route to another is subject to tremendous errors, and caution is advised when doing so. Default values are, therefore, not recommended and conversion factors must be calculated for each individual situation, making appropriate assumptions about body weight, minute volume, percentage deposition, retention and absorption, also taking into account pulmonary and extrapulmonary pathomechanisms as well as the exposure regimen used in the bioassay and that of actual interest. Also with systemically acting agents caution is advised to perform simple route-to-route extrapolations in the absence of a detailed pharmacokinetic understanding and knowledge of the critical toxophoric moieties.

Keywords: Route-to-route extrapolation; Rodent inhalation studies; Non-rodent inhalation studies; Portal-of-entry effects

1. Introduction

Throughout the world regulatory agencies have focused their emphasis on promoting workplace safety. To achieve this objective, inhalation studies are a basic prerequisite. Despite of this, many of the required toxicology studies mirror requirements that address continuous dosing through the oral route. Thus, many of the toxicology studies available are not designed with worker, applicator or end-user risk assessment in mind. For instance, worker exposure to agrochemical pesticides tends to be intermittent in nature, and mainly via the dermal route. However, specific use patterns are associated with exposure via the inhalation route (Krieger and Ross, 1993; Ross et al., 2001). With respect to pesticides used in residential areas in order to control and extinguish pests, non-occupational low-level, long-term exposure via the inhalation route may be of concern. Because of the regulatory focus on dietary expo-

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sure, risk assessment for occupational settings is often driven by toxicological data generated in laboratory animals with a disparate route, frequency, duration and magnitude of exposure. Yet, almost all of the required toxicity studies utilize the oral exposure route for dosing. By default, the concept of aggregating fractional exposure doses into one total body burden is given preference to assessing route-specific no-observed-adverse-effect levels (NOAELs) or for inhalation studies no-observed-adverse-effect concentrations (NOAECs). Clearly, the differences in routes, associated with intermittent exposure regimens, result in dissimilar toxicokinetics and substance-specific toxicodynamics, raising questions about the accuracy of the commonly applied procedures. In spite of the great deal of uncertainty involved in this process, these data are used in assessing the critical body burden without taking into account the exposure metric required to elicit a given toxicological effect. Examples of exposure metric considerations include not only focusing on estimates of route-specific aggregate exposures of the active agent during the time period of interest (a NOAEL may be based on concentration-dependent portal-of-entry, local responses or total body burden related systemic effects) they have also to address potential effects elicited by the inert ingredients commonly present in end-user products. When tested in the laboratory the dose metrics may change from high-concentration exposure scenarios, where the test agent is present as an aerosol, to low-level exposure environments, where exposure is commonly to the vapor phase. In addition to exposure to the active agent per se, workers exposed to these substances may inhale carrier substances, emulsifiers and stabilizing agents, solvents or propellants. Opposite to studies utilizing non-inhalation routes of exposure, following mechanical aerosolization (dispersion) of pesticide formulations the relative composition of the formulation may change dramatically when airborne because of difference in transfer efficiencies of volatile and non-volatile constituents. This paper will consider some of the essential features of portal-of-entry related damage and the potential pitfalls involved in dosimetry and route-to-route extrapolations.

2. Principle structures of the respiratory tract

When an organ system is as complex as the respiratory tract, it is convenient to simplify it by forming conceptual anatomic units or 'compartments'. Conventionally one may think in terms of three major compartments, which divide the respiratory tract into regions based upon anatomical features, upon particle deposition and clearance phenomena that occur within the tract and are specific to each compartment. The regions are called the nasopharyngeal (NP), the tracheobronchial (TB), and the pulmonary (P). The NP compartment begins at the anterior nares and includes the respiratory airway down to the level of the larynx. The deposition of inhaled substances does not occur uniformly along all airways. Specific patterns of enhanced local deposition within the respiratory tract are important in determining dosage, since the latter depends on the surface density of deposition. Nonuniformity implies that the initial dose delivered to specific sites may be greater than that occurring if a uniform density of surface deposit is assumed. This is especially important for inhaled particles that affect the tissue on direct contact, such as irritants. For large particles (>5 μm aerodynamic equivalent diameter in humans), the predominant deposition mechanism in the extrathoracic region (head airways region) is inertial impaction. The mechanisms affecting the transport and deposition of gases involve convection, diffusion, absorption, dissolution, and chemical reactions. In this region, deposited and relatively soluble material is rapidly cleared into the blood, while for poorly soluble agents physical clearance by mucociliary transport to the throat for subsequent swallowing is predominant. The effective removal of insoluble particles may require 1–2 days. The nasal passages of small laboratory rodents are highly tortuous and are lined with four distinct nasal epithelial populations in most animal species. This includes squamous, transitional, and pseudostratified respiratory epithelium in the anterior aspect of the main nasal chamber; and olfactory epithelium, which is metabolically the most active epithelium in this region, located in the dorsal aspect of the nasal cavity.

After chemical exposure, reflex mechanisms may be invoked in order to protect an individual from inhaling excessive concentrations of the respective chemical. When inhaled through the nose, chemicals capable of stimulating the trigeminal nerve receptor will evoke a burning sensation of the nasal passages. Currently, a clear distinction cannot be made between 'nuisance' and mere perception or awareness of exposure and related somatic health effects such as headache. The onset of the response, that is, the decrease in breathing frequency in small laboratory rodents, is usually observed within a few minutes and is characterized by a stereotypic bradypneic pause during the expiratory phase of respiration (Alarie, 1966, 1973, 1981). As illustrated in Fig. 1, in bioassays using rodents a sustained decrease in ventilation may reduce the inhaled dose appreciably. Chemosensory effects of stimulation can either be irritative or odorous. Stimulation of the olfactory nerve and the trigeminal nerve results in sensation of smell, whereas stimulation of the trigeminal nerve gives rise to chemical irritation or intranasal chemesthesis, which is the activation of the trigeminal, glossopharyngeal, or vagal nerves via chemical stimulation. Historically, there have been attempts to segregate chemicals into categories of pure olfactory and pure trigeminal stimulants, although it is now conceded there are very few chemicals that fall into either category exclusively. Because most agents, at sufficient concentrations, elicit both olfactory and trigeminal activation, it is important to understand the normative function and interactions of these two systems, as well as the clinical and experimental methods used to assess and quantify odor and sensory irritation that can result from exposure to airborne chemicals or pesticides (Kendal-Reed, 2001; Feron et al., 2001; Meldrum, 2001). Animal models utilizing this endpoint were established to determine to relative potency of pyrethroid aerosols to elicit paresthesias (Pauluhn, 1998; Pauluhn and Machemer, 1998).

In experimental animals it has been shown that metal ions commonly impermeable to the blood–brain barrier may pass the brain via olfactory receptor neurons from the nasal lumen through the cribriform plate to the olfactory bulb. Some metal ions (e.g. Mn, Zn) known to occur in organometallic fungicides or airborne particulates in ambient air can cross synapses in the olfactory bulb and migrate via secondary olfactory neurons to distant nuclei of the brain. After inhalation uptake of a metal-containing solutions, transport of the metal via olfactory axons can occur rapidly, within hours or a few days (e.g. Mn), or slowly over days or weeks (e.g. Ni). The olfactory bulb tends to accumulate certain metals with greater avidity than other regions of the brain. The molecular mechanisms responsible for metal translocation in olfactory neurons and deposition in the olfactory bulb are unclear, but complexation by metal-binding molecules may be involved (Sunderman, 2001).

The TB region begins at the larynx and includes the trachea and the ciliated bronchial airways down to and including the terminal bronchioles. A relatively small fraction of all sizes of particles, which pass through the NP region, will deposit in the TB region. The mechanisms of inertial impaction at bifurcations, sedimentation, and for small particles, Brownian diffusion cause TB deposition. Interception can be an important deposition mechanism for fibrous dusts. During mouth breathing of aerosols the benefits of the collection of larger particles in the nose are lost and these larger particles tend to deposit in the TB region with high efficiency. An important characteristic of the TB region is that this region is both ciliated and equipped with mucus secreting elements so that clearance of deposited poorly soluble particles occurs rapidly by mucociliary action to the throat for swallowing. Again, relatively soluble material may rapidly enter the blood circulation. The rate of mucus movement is slowest in the finer airways and increases toward the trachea. Since particles depositing in the TB tree are probably distributed differently with respect to size, with smaller particles tending to deposit deeper in the lung, one expects larger particles to clear more quickly.

The third compartment, the P or pulmonary region, includes the functional gas exchange sites of the lung. The most prominent structure in this region is the alveolus. Each alveolus in the lung parenchyma opens directly into an alveolar duct or sac. Alveoli and alveolar ducts arising from a

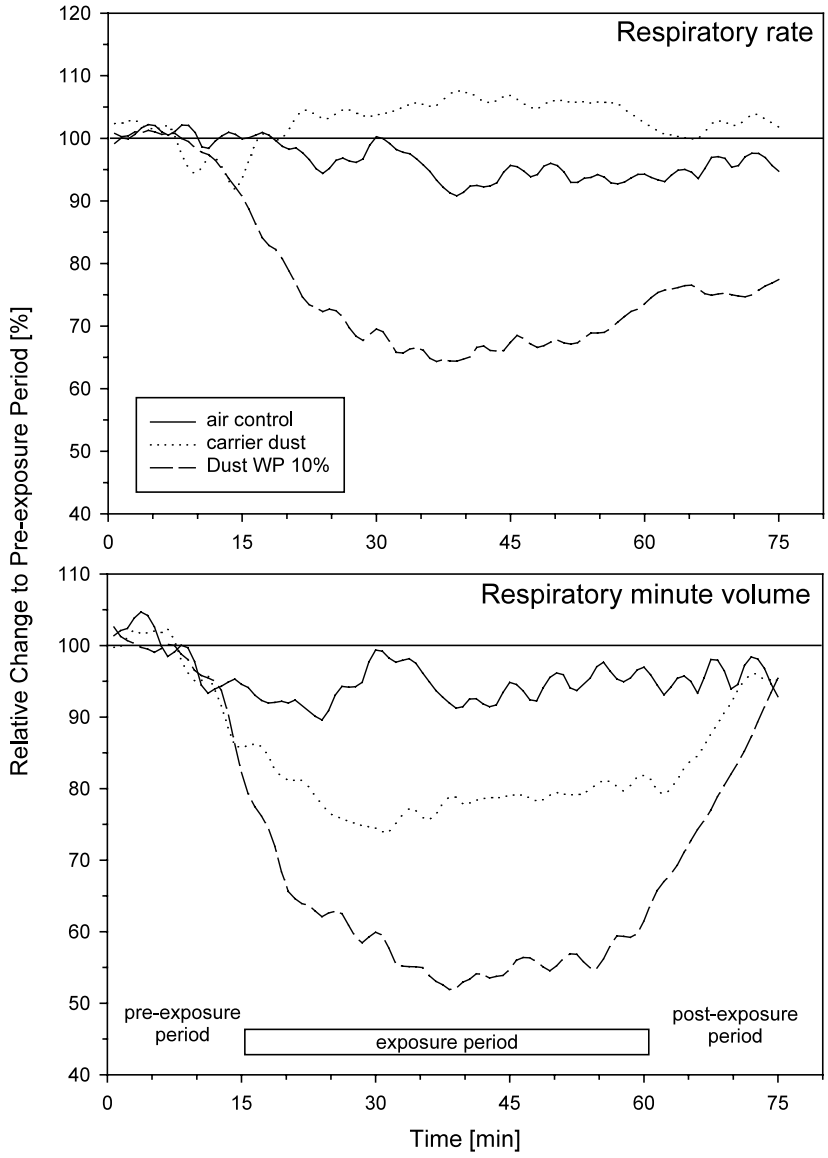

Fig. 1. Recording of respiratory rate and minute volume of rats nose-only exposed in volume displacement plethysmographs. For exposure a directed-flow nose-only inhalation chamber was used. Measurements were made in four rats simultaneously using the following sequence: pre-exposure to air, exposure to either air (control), approximately 70 mg/m^3 of carrier dust or dust containing 10% of a Type II pyrethroid (WP 10%), post-exposure to air. Pre-exposure data are normalized to 100% and effects evoked by the test substance are expressed as relative change to the pre-exposure period.

single conducting airway constitute a pulmonary acinus. A thin tissue barrier-consisting of type I and type II alveolar cells which represent approximately 25% of all the cells in the alveolar septum-provides an extremely efficient means of gas transfer over a large surface area (Fig. 2). Type I cells cover a large surface area of the lung parenchyma (ca. 90% of the alveolar surface). In regard to number, there are more pneumocyte Type II cells than Type I (67:33%). Preferential damage to type I cells by various agents may be explained by the fact that this cell type constitutes

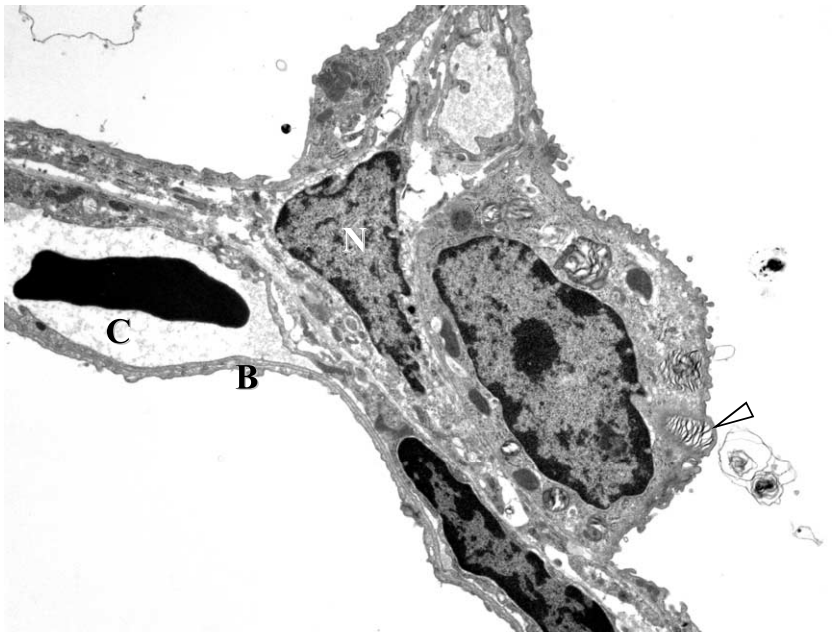

Fig. 2. Ultrastructural photograph of the septal region of a rat lung. The alveolus is separated from the blood capillary (C), which contains an erythrocyte, by a thin margin of the Type I cell. The air–blood barrier constitutes a three barrier system, that is the capillary endothelium, the basal membrane and the Type I pneumocyte (B). Note that the thickening of the interstitial space is confined to the top of the capillary (the 'service side') while the total alveolar-capillary membrane remains thin on the bottom side (the 'active side'). The type II cell can be seen containing lamellar bodies (arrowhead), the storage form of the pulmonary surfactant synthesized in this cell. N, nucleus.

a vulnerable target because of its large surface area in relation to cell mass. Type II cells are cuboidal, show abundant perinuclear cytoplasm, maintain an ion gradient within the lining fluids so that extravasated fluid is efficiently removed from the alveoli, are metabolically active and produce surfactant. In the case of damage to the type I epithelium, they may undergo mitotic division and replace damaged cells. The integrity of the delicate alveolar septa is maintained in large measure by a network of mesenchymal interstitial cell populations that produce collagen and elastin fibers. Surface tension at the air/water interface produces forces that tend to reduce the area of the interface leading eventually to a collapse of alveoli. It also reduces the pressure gradient between the vascular system (high hydrostatic pressure) and alveolus (subatmospheric pressure), thus preventing extravasation of plasma into the alveolus (Nieman, 1985; Bhalla, 1999; Vesterberg et al., 2001). In regard to the inhalation toxicity of respirable aerosols containing surface active substances they may potentially damage the blood–air barrier through a physical mode of action leading to an increased extravasation of plasma into the alveoli that can not occur by non-inhalation routes. When damaged excessively, alveolar flooding, i.e. lung edema occurs.

3. Pitfalls of route-to-route extrapolation

The route, duration and frequency of human exposure to a substance during normal use (and, as appropriate, reasonably foreseeable misuse) need to be taken into account when evaluating the data for hazard identification: hazards which may not be expressed under one exposure scenario but may become apparent under another. When data are lacking for a relevant route of human exposure, the possibility of using route-to-route extrapolation may be considered but, in general, route-to-

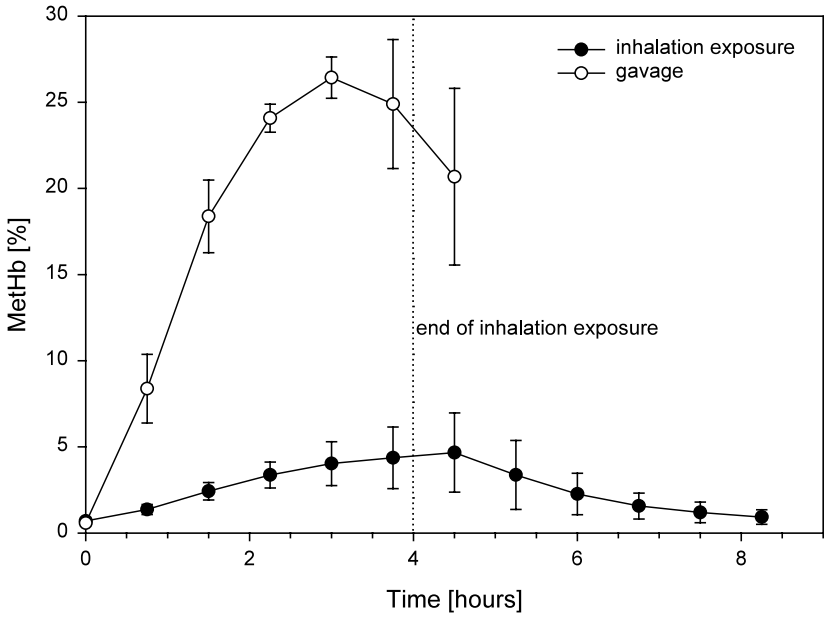

Fig. 3. Time-course of methemoglobin (MetHb) formation in beagle dogs head-only exposed to the volatilized atmosphere of aniline for 4-h. The mean exposure concentration was 174 mg/m^3 air. After complete recovery, the dogs received an equivalent of the calculated dose (15 mg/kg bw) by gavage. Blood was collected repeatedly in 45-min intervals commencing with the onset of exposure. Data represent mean $\pm$S.D. ($n = 4$).

route extrapolation is thought to be a poor substitute for toxicity data obtained using the appropriate route of exposure. However, some pragmatic approaches to calculating an approximate NOAEL (or NOAEC in terms of inhalation toxicology) by extrapolation have been used, when specific data are not readily available, to facilitate decision taking with regard to the potential need to ensure control of exposure, or to obtain further data, for a particular route of exposure. The methods described below are for extrapolating from oral toxicity data since this is the route most often used for repeated dose toxicity studies in animals. A number of publications are available which provide guidance on route-to-route extrapolation (Gerrity and Henry, 1990; Andersen et al., 1992; Pepelko and Withey, 1985).

In the case of systemically acting substances, there are possibilities for extrapolation from one exposure route to another. However, it requires an understanding of the toxicokinetic and toxicodynamic principles involved. Empirical correlations are often used to evaluate the relationship of dose and response with little appreciation of the detailed biological interactions of the test agent. The main obstacles are differences in the degrees and rates of absorption by different exposure routes and differences in biotransformation, particularly in the case of first-pass metabolism occurring in the gastrointestinal tract or liver. For example, when such extrapolations are attempted for aniline this process may be prone to marked errors because aniline belongs to that group of substances known to be activated by a first-pass gastrointenstinal and hepatic metabolism. The activation of aniline and the ensuing methemoglobin (MetHb) formation and reduction has been described to be a multistep process (Kiese, 1974; Akintowa, 2000). Likewise it can be assumed that both the kind of dosing regimen as well as the rate of dose-delivery have major impact on the magnitude of the MetHb levels produced. The time-course of MetHb formation in beagle dogs head-only exposed to a volatilized atmosphere of aniline for 4-h demonstrates that the ostensibly equal oral dosage (15 mg/kg by gavage) elicits five times

higher MetHb levels as compared with inhalation (exposure to an actual breathing zone concentration of 174 mg/m^3, duration of exposure 4 h (Fig. 3). When using the default respiratory minute volume of dogs of 0.36 l/kg-min the total exposure dosage (0.36 l/kg-min × 240 min × 0.174 mg/l = 15 mg/kg) mirrors exactly that administered by gavage (Pauluhn, 2002). Thus, for agents known to be bioactivated by a hepatic first-pass metabolism, the conversion of findings obtained from oral dosing to inhalation exposure concentrations is subject to overestimate dramatically the magnitude of MetHb formation likely to occur following inhalation exposure. As to whether the fivefold lower potency by inhalation is solely related to the hepatic first-pass bioactivation, the rate of delivery or also to a less than 100% retention of the inhaled vapor within the respiratory tract remains to be elucidated.

Moreover, in contrast to studies where the uptake is by the gastrointestinal route, the extent of pH- and passage time-dependent degradation of modification of the test agent may be decisive for the outcome of study. Thus, the formation of new toxicophoretic entities and portal-of-entry specific types of toxicities, including site-specific, often rate-dependent compensatory mechanisms need to be envisaged before attempting such extrapolations. Furthermore, for such a local modes of action the dose to the target tissue at first contact will be determined by the kinetics of formation and elimination or scavenging of the toxicophoretic moiety rather than systemic bioavailability of the parent substance. For instance, the uptake of metal ions via the GI-tract is, to a great extent, homeostatically controlled whereas in the alveolar region metal ions may prompt a series of responses specific to this region. Accordingly, toxic species formed in the gastrointestinal tract may not necessarily be formed following inhalation. Upon inhalation, such primary responses are commonly restricted to the pulmonary region, ranging from the mere influx of alveolar macrophages (removal of poorly-soluble particulates) up to the local induction of scavenger proteins, such as metallothionein (MT), and the anti-protease or anti-oxidant systems. These examples demonstrate that for substances having any local mode of action at the portal-of-entry, that is within the respiratory or gastrointestinal tract, extrapolations from one route to another will often be misleading with respect to effective dose and probably even the nature of the effect. The calculation of 'systemic total body burden' based on such localized responses occurring at the initial contact may lead to erroneous conclusions.

One of the commonest problems in route-to-route extrapolation relates to the assumption that equal doses via the inhalation and oral routes may be regarded to be equitoxic. This approach is challenged using data from both acute and subchronic studies of pesticides utilizing either route of exposure. To make comparison of the oral and inhalation data possible, inhalation data are converted to inhalation dosages by using a default respiratory minute volume per kg bw of 0.75 l/min kg bw (Mauderly, 1986) {inhalation dose = exposure concentration (mg/m^3) × respiratory minute volume per kg bw × exposure duration}.

Based on data of organophosphates known to inhibit actylcholinesterase a comparison of oral LD_{50} data and calculated inhalation LD_{50} data was based on actually available LC_{50} values (Storm et al., 2000). For equal toxic potency, the ratio of oral LD_{50}/inhalation LD_{50} (calculated based on the inhalation LC_{50}) is equal to 1. The comparison made in Fig. 4 suggests that substantial deviations from expectation occur, in spite of the quite similar toxic principle of the organophosphate pesticides. At the ends of lower and higher toxic potencies (see Fig. 4), the ratios were smaller and higher, respectively, indicating that the active substance is either more toxic by the oral route than by inhalation for very toxic organophosphates or more toxic by inhalation than by oral administration for the less toxic organophosphates. Notionally, the more toxic ones appear to act more rapidly so that maximum cholinergic toxicity is more pronounced using a bolus administration when compared with the longer dosing intervals used in inhalation studies.

The NOAECs from repeated exposure guideline inhalation studies with pesticide aerosols (exposure 6 h/day on 5 days/week for 3 or 4 weeks) are converted to inhalation dosages as described above and compared with the NOAELs from subacute

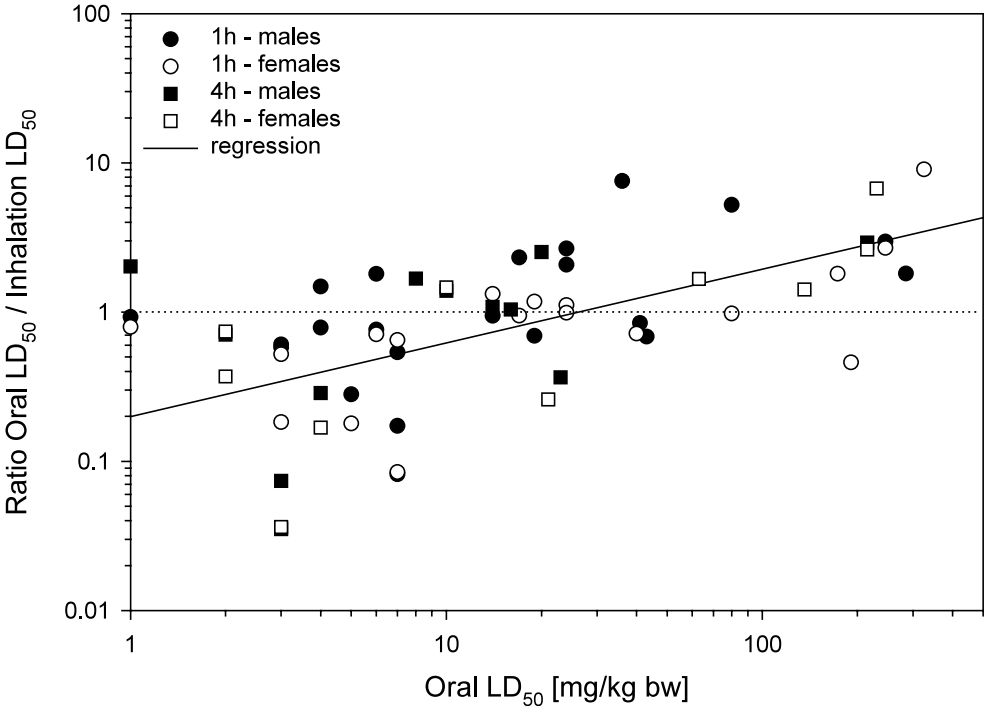

Fig. 4. Comparison of acute lethal toxic potency data of organophosphate pesticides in rats following a single 1 or 4-h inhalation exposure (LC_{50}) or oral administration (LD_{50}) (LD_{50} and LC_{50} data were from Storm et al. (2000). To make comparisons possible, exposure concentrations were converted to inhalation LD_{50} dosages.

or, if not available, subchronic oral studies (4-week feeding or gavage: 71%, $\geq$13-week dietary studies: 29%; $n = 42$) with the same pesticide. As depicted in Fig. 5, the overwhelming fraction of the ratios of NOAELs from oral and inhalation studies with various types of pesticides are in a range of 1–10 and ≥ 10 when the most critical endpoint (lowest (NOAEC) was based on systemic and lung-specific local effects, respectively. In spite the fact that 29% of the NOAELs stemmed from oral studies of appreciably longer duration than the 3 or 4 weeks inhalation studies compared with, in many cases, the prediction of inhalation NOAELs based on oral studies is biased to underestimate conspicuously the toxic potency of inhaled substances. From the data summarized in Fig. 5 one may deduce that the level of uncertainty involved in the process of risk characterization is significantly reduced in the presence of actual inhalation data.

4. Conclusions

The conversion from oral routes to ostensibly equipotent inhalation exposure concentrations is subject to both marked overestimation and underestimation in the absence of the following toxicokinetic data, whether a substance has local irritant properties at the portal-of-entry, whether it is degraded to new toxicophoretic entities within the gastrointestinal tract, whether it is bioactivated or detoxified either within the gastrointestinal tract or in the hepatic first-pass metabolism, and whether the critical mode of action is total-dose or dose-rate dependent. Extrapolations from one dosing regimen, e.g. oral administration of bulk doses to workplace-like exposure regimens, are not reliable without consideration of these aspects. Default values for the conversion from oral to inhalation are contingent upon many mechanistic and substance-related factors, which may invali-

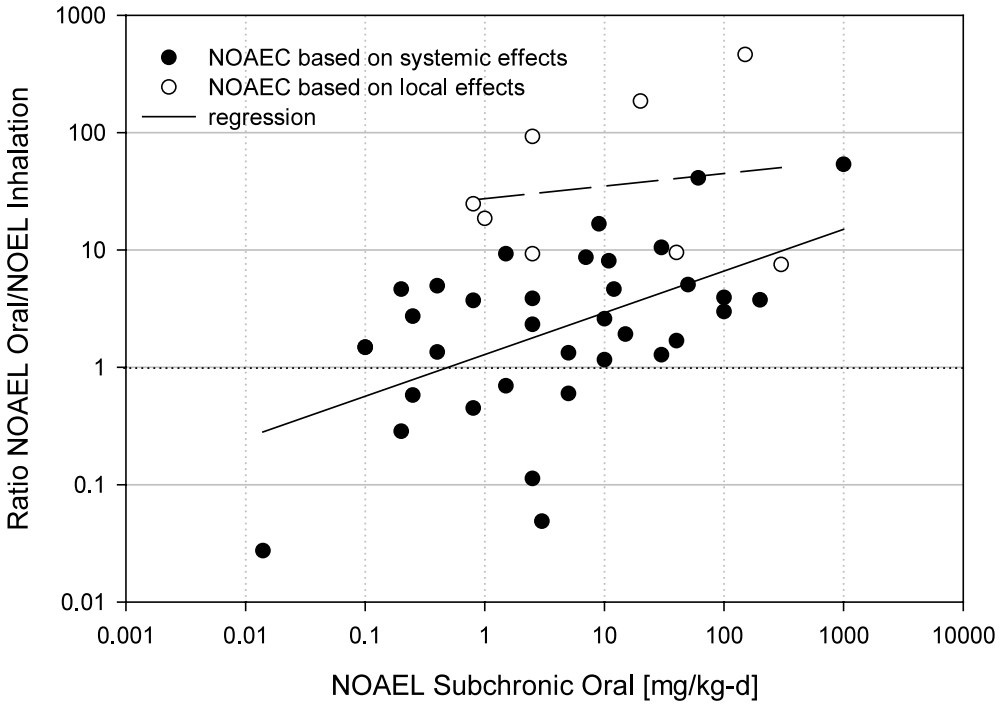

Fig. 5. Comparison of NOAELs of various types of pesticides in rats from subacute inhalation and subacute/subchronic oral (dietary or gavage) studies in rats. To make comparisons possible, NOAECs from inhalation studies were converted to inhalation dosages (NOAELs).

date the use of simple default assumptions. Biologically based modeling, which takes into account specific mechanistic steps governing tissue disposition and toxic action may lead to better predictions. Accordingly, the choice of an appropriate measure of 'dose' in inhalation toxicity studies must be defined by the nature of the pathogenesis process, i.e. defined according to the mechanism of action for the effect under consideration. Acute inhalation studies (LC_{50} per se) appear to be a poor predictor of the NOAEC following repeated inhalation exposure with the exception of agents exhibiting a low chronicity index and being highly toxic, e.g. were the limiting factor of toxicity can be related to a single target or is solely dependent on a local irritant threshold concentration. The evolution of an integrated chemical–biological concept of dose will continue as the sophistication in examining toxicological problems is enhanced by improved mechanistic understanding of a variety of toxic phenomena at the molecular, cellular, animal model and human level.

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