BACKGROUND: The RD50 (exposure concentration producing a 50% respiratory rate decrease) test evaluates airborne chemicals for sensory irritation and has become an American Society for Testing and Materials (ASTM) standard method. Past studies reported good correlations (R²) between RD50 and the occupational exposure limits, particularly threshold limit values (TLVs).

OBJECTIVE: The main purpose of this study was to examine the relationship between RD50 and human sensory irritation responses in a quantitative manner, particularly for chemicals that produce burning sensation of the eyes, nose, or throat, based on lowest observed adverse effect levels (LOAELs) reported for human subjects.

METHODS: We compared RD50 with LOAELs and acute reference exposure levels (RELs). RELs, developed by the California Environmental Protection Agency’s Office of Environmental Health Hazard Assessment, represent a level at which no adverse effects are anticipated after exposure. We collected RD50s from the published literature and evaluated them for consistency with ASTM procedures. We identified LOAELs for human irritation and found 25 chemicals with a corresponding RD50 in mice.

DISCUSSION: We found the relationship between RD50 and LOAELs as log RD50 = 1.16 (log LOAEL) + 0.77 with an R² value of 0.80. This strong correlation supports the use of the RD50 in establishing exposure limits for the public. We further identified 16 chemicals with both RD50 and corresponding acute RELs, and calculated the relationship as log RD50 = 0.71 (log REL) + 2.55 with an R² value of 0.71. This relationship could be used to identify health protective values for the public to prevent respiratory or sensory irritation.

CONCLUSION: Consequently, we believe that the RD50 has benefits for use in setting protective levels for the health of both workers and the general population.

KEY WORDS: Alarie test, exposure levels, LOAEL, RD50, REL, sensory irritation, TLV, Environ Health Perspect 115:1609–1616 (2007). doi:10.1289/ehp.9848 available via http://dx.doi.org/ (Online 7 August 2007)

Evaluation and Application of the RD50 for Determining Acceptable Exposure Levels of Airborne Sensory Irritants for the General Public

Yu Kuwabara, George V. Alexeeff, Rachel Broadwin, and Andrew G. Salmon

Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, California, USA

Although airborne chemicals can cause a number of harmful effects, the most common effect is sensory irritation (De Ceaurriz et al. 1981). Exposures to a sensory irritant may stimulate the trigeminal nerve endings and laryngeal receptors, eliciting any one or a combination of the following symptoms: burning sensation of the eyes, nose, or throat, as well as coughing sensations (Alarie et al. 2000). Sensory irritation is also the most common end point for occupational exposure levels (OELs). For one specific OEL measure, threshold limit values (TLVs) [developed by the American Conference of Governmental Industrial Hygienists (ACGIH 2006)] are calculated based on sensory or pulmonary irritation for > 50% of the compounds. Kane et al. (1979) reported that approximately two-thirds of the compounds for which they found a TLV acted as sensory irritants. A qualitative evaluation of sensory irritants indicated that sensory irritation responses in the mouse are predictive of responses in humans (Alarie 1973a).

In 1966, Alarie initially proposed the use of an animal test to evaluate the potency of airborne sensory irritants. The bioassay uses male Swiss-Webster mice to measure decreases in respiratory frequency resulting from exposure to a geometric series of concentrations of airborne irritants (Alarie 1966). The concentration inducing a 50% decrease in respiratory frequency is termed the RD50. From these measured RD50s, Alarie (1981b) ranked irritant potencies and found a good correlation (R²) between RD50 and TLVs. The Alarie test evolved over the years and was adopted in 1984 as a standard test by the American Society for Testing and Materials (ASTM 2004). The “RD50 test” or the “Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals” (ASTM 2004) quantitatively measures irritancy as indicated by the reflex inhibition of respiration in mice exposed to sensory irritants. For the test, four mice are first acclimatized to the chamber and are then simultaneously exposed to the airborne chemical. A sufficient number of groups are exposed to a geometric series of concentrations so that a concentration–response curve can be constructed from the analysis. The mice are placed in a body plethysmograph attached to an exposure chamber so that only the head is exposed to the test material. The plethysmographs are connected to pressure transducers, which sense changes created by inspiration and expiration. The amplified signals are transmitted to a polygraph recorder. The concentration of airborne irritant that produces an RD50 is determined from the concentration–response curve constructed from the various data points obtained with a series of concentrations.

Sensory irritation is a reflex reaction from stimulation of the trigeminal or laryngeal nerve endings (Boylstein et al. 1996). The sensory irritant response is mediated through binding to the trigeminal nerve receptors and appears to follow Michaelis-Menten receptor kinetics. Although the RD50 concentration has been described as “intolerable” to humans, as indicated in the ASTM standard, “the test method will detect irritation effects at concentrations far below those at which pathological changes are observed” (Alarie 2000; ASTM 2004). Further, as demonstrated by Barrow et al. (1986), pathologically detectable responses are expected only after prolonged repeated exposure.

RD50s are a basis, at least partially, for a number of OELs by ACGIH (ACGIH 2006). The calculation methodology is based on Kane et al. (1979), who evaluated data from 11 sensory irritants and concluded that a level one-hundredth of the RD50 would produce “minimal or no sensory irritation” in humans. The current suggestion of setting OELs at 0.03 RD50 comes from Alarie (1981a, 1981b), because 0.03 RD50 is halfway between 0.1 RD50 and 0.01 RD50 on a logarithmic scale. Alarie (1981a) reported a strong correlation (R² = 0.89) between 0.03 RD50 and OELs for the 26 chemicals tested. Subsequently, both analyses, one using 41 chemicals (Alarie and Luo 1986) and most recently another using 89 chemicals (Schaper 1993), resulted in a lower but still strong correlation (R² = 0.78). Although most of the
applications of the RD₅₀ have focused on OELs. Nielsen et al. (1995) found that protection against indoor sensory irritation effects could be achieved at a level of 0.025–0.25 of the OEL. Multiple studies show strong correlations between RD₅₀ and OELs, supporting the continued use of the Alarie test for establishing OELs (Kane et al. 1979, 1980; Schaper 1993).

In this study we examined the relationship between RD₅₀ and human sensory irritation responses in a quantitative manner, particularly for chemicals that produce burning sensation of the eyes, nose, or throat, based on lowest observed adverse effect levels (LOAELs) reported for human subjects. We also analyzed the relationship between RD₅₀ and OELs for identified human sensory irritants. Finally, we evaluated the relationship between RD₅₀ and acute reference exposure levels (RELS) developed to protect the public (Collins et al. 2004). RELs are defined as “[t]he concentration level at or below which no adverse health effects are anticipated for a specified exposure duration [1 hr for the acute RELs]. … RELs are based on the most sensitive, relevant, adverse health effect reported in the medical and toxicological literature.” A strong correlation between RD₅₀ and LOAELs, TLVs, and acute RELs will support the use of RD₅₀ in establishing guidance levels to protect the public from sensory irritants.

Methods

LOAELs versus RD₅₀. Using published toxicologic studies of human subjects exposed to sensory irritants, we identified human LOAELs. Criteria for selecting human LOAELs required that the studies describe mild irritating effects (Alexeeff et al. 2002) resulting from acute inhalation exposure. Published human studies on hazardous air pollutants (HAPs) served as the primary sources of information for these chemicals (Alexeeff et al. 2002). We searched PubMed (National Library of Medicine; http://www.ncbi.nlm.nih.gov/sites/entrez), Biosis (www.biosis.org/), Current Contents (http://scientific.thomson.com/products/ccc/), Toxline (National Library of Medicine; http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE), SciFinder Scholar (Chemical Abstracts Service; http://www.cas.org/support/scif/sfsolutions/index.html), Oldmedline (http://www.nlm.nih.gov/databases/databases_oldmedline.html), Web of Science (http://scientific.thomson.com/products/wos), and Environmental Sciences and Pollution Management Databases (Cambridge Scientific Abstracts; http://www.csa.com/factsheets/envclust-set-c.php) to identify toxicologic studies published between 1970 and 2005 for all 189 HAPs. Search terms included the chemical name, the type of LOAEL effects (e.g., irritation), route of exposure (inhalation), and exposure duration (acute). We also conducted online searches for additional non–HAP chemicals with an identified RD₅₀. Further, we conducted manual searches from secondary sources through 2005. Five criteria were developed for inclusion of a study in the analysis: a) peer-reviewed and published, well-conducted industry-sponsored studies or doctoral dissertations; b) inhalation exposure; c) discrete acute exposure; d) available LOAEL for a mild adverse health effect; and e) the original research. For each human study analyzed, information about the chemical, exposure time, end-point category (eye and/or respiratory irritation), and LOAELs were recorded. If multiple mild responses were reported at various dose levels for the same chemical and exposure time, then the lowest adverse effect level was considered the LOAEL.

RD₅₀. We evaluated only the data for non–Swiss-Webster mice and excluded studies with rats in this analysis.

In cases where both RD₅₀ and human LOAELs were available for the same chemical, we log transformed and fit the data with a linear relationship using Microsoft Office Excel 2003 (Microsoft, Redmond, WA) and SAS version 9.1 (SAS Institute Inc., Cary, NC) for Windows. This procedure was similar to previous RD₅₀ comparisons (e.g., Alarie 1981b). When we found multiple LOAELs or RD₅₀ for a single chemical, we considered each reported value in the analysis. Sensitivity analyses were conducted by evaluating the correlation generated from the regression of LOAELs with RD₅₀ value data sets, which varied by exposure time, or strain tested. We also conducted subanalyses using upper and lower respiratory tract effects.

RELS versus RD₅₀. As reported by Collins et al. (2004), the California Environmental Protection Agency (EPA) has developed 51 acute irritation RELs. We evaluated these RELs to identify those based on eye or respiratory irritation end points in humans, and compared with RD₅₀. Using Microsoft Office Excel 2003 (Microsoft) and SAS version 9.1 (SAS) for Windows, we log transformed and fit the data with a linear relationship.

TLVs versus RD₅₀. For all RD₅₀ used in the above analyses, we identified TLVs from ACGIH (2006). The TLVs included time-weighted averages, short-term exposure limits and ceilings. If the documentation reported more than one TLV value, we used the lowest, more protective value. A third comparison between RD₅₀ and TLVs of identified human irritants, based on identification of a human LOAEL for irritation, was conducted using log-transformed data, fit with a linear relationship, and analyzed with Microsoft Office Excel 2003 (Microsoft) and SAS version 9.1 (SAS) for Windows.

Results

LOAELs versus RD₅₀. From our search, we identified 25 chemicals with 72 human acute irritation LOAELs from 49 studies (Table 1). The adverse effects, exposure times, and information reflecting the quality of the study (e.g., placebo-control, blinding, subject selection, subject characteristics, exposure design, and data reporting) are indicated in Table 1. For the 25 chemicals identified, 63 RD₅₀s were found in mice (Table 2). The RD₅₀s were based on seven mouse strains and exposure times ranging from 5 to 180 min.

Figure 1 shows the correlation between RD₅₀ and LOAELs for all RD₅₀s identified in all strains of mice for the 25 chemicals, allowing for 198 comparisons. There is a strong overall correlation (R² = 0.80) between RD₅₀ and human irritation LOAELs. When we conducted the analysis for Swiss-Webster mice only (Table 3), we were able to include 75 data points for 19 compounds, and the correlation decreased slightly (R² = 0.74). When we evaluated only the data for non–Swiss-Webster mice (Table 3), there was little change in the correlation (R² = 0.83). We conducted several subanalyses to consider the influence of the RD₅₀ study exposure duration. As indicated in Table 3 there was little influence on the R². Thus, according to this analysis, the strain of mouse tested does not appear to affect this evaluation substantially. The equations do not change significantly, and the correlation is still significant for all analyses, validating the inclusion criteria used. As indicated in Table 3, we also considered several subanalyses to address the influence of the human LOAEL variability. Specifically, we considered the issue of LOAEL sensitivity, the type of irritation end point, study quality, and the duration of exposure for the human LOAEL. The only significant effect on the correlation was observed when considering human irritation end points of the lower respiratory tract; the poor R² appears to be attributed partly to the few number of data points (29) in the analysis.

RELS versus RD₅₀. From the 51 California acute RELs, we identified 16 that had irritation as their end point and a corresponding RD₅₀.
### Table 1. LOAELs for human sensory irritation for each study found in the literature.

| Compound                        | LOAEL (ppm) | Time (min) | No. of subjects | % Response | End point | Reference                              |
|---------------------------------|-------------|------------|-----------------|------------|-----------|----------------------------------------|
| Acetaldehyde                    | 12          | 4–9        | 27              | 0          | Eye irritation  | Stephens et al. 1961                   |
| Acetone                         | 300         | 3–5        | 10              | Majority   | Eye irritation | Nelson et al. 1943                     |
| Allyl alcohol                   | 0.78        | 5          | 6               | Average    | Eye irritation | Hene-Trboch et al. 1977                 |
| Ammonia                         | 5           | 180        | 12              | 100        | Eye irritation | Sundblad et al. 1986                   |
| n-Butanol                       | 25          | 3–5        | 10              | Majority   | Eye, nasal, and throat irritation | Nelson et al. 1943                     |
| Chlorine                        | 0.95        | 240        | 8               | Average    | Forced vital capacity decrease (L) | Rotman et al. 1983                     |
| Ethyl acetate                   | 400         | 3–5        | 10              | Majority   | Nasal and throat irritation | Nelson et al. 1943                     |
| Ethylene                       | 1.4         | 17         | 3               | Average    | Eye irritation | Stephens et al. 1961                   |
| Formaldehyde                    | 0.6         | 3–5        | 6               | Majority   | Eye irritation | Silverman et al. 1946                   |
| Isocyanate                      | 0.5         | 30         | 5               | 100        | Eye irritation | Stephens et al. 1961                   |
| Methyl isocyanate               | 0.5         | 3–5        | 10              | Majority   | Eye irritation | Nelson et al. 1943                     |
| Nitrogen dioxide                | 1.5         | 180        | 15              | Average    | Increased airway resistance (L) | Frampton et al. 1991                   |
| n-Butanol                       | 25          | 3–5        | 10              | Majority   | Eye irritation | Nelson et al. 1943                     |
| n-Pentanol                      | 100         | 3–5        | 10              | Majority   | Eye irritation | Nelson et al. 1943                     |
| n-Pentyl acetate                | 100         | 3–5        | 10              | Majority   | Eye irritation | Nelson et al. 1943                     |
| p-Xylene                       | 100         | 450        | 11              | 100        | Eye and respiratory irritation | Hake et al. 1981                      |

**Abbreviations:** FEV1, forced expiratory volume in 1 sec; NG, not given. For some studies, multiple experiments were conducted with different exposure times or endpoints resulting in multiple LOAELs for the compounds.  
*Numerical values indicate the percent of subjects responding. *End points with (L) depict “Lower” respiratory end points; all others are “Upper” respiratory end points. *Average* indicates that the response was a mean response. *Study was considered to be of higher quality due to study design (e.g., placebo-controlled, blinding, subject selection, subject characteristics, exposure conditions, and/or data reporting).
Figure 2 indicates a good correlation ($R^2 = 0.71$) between RD50s and RELs for 16 chemicals with 37 comparisons.

**TLVs versus RD50s.** For the compounds identified with RD50 and LOAELs, 24 had a corresponding TLV. Figure 3 shows the correlation of TLVs to RD50s with an $R^2$ value of 0.81. Thus, when focusing specifically on human irritants, the relationship between the TLV and RD50 remains strong.

**Conclusions**

The focus of this paper is on the applicability of RD50s for human health risk assessment. Exposure guidelines to protect workers and the public often focus on mild irritating signs or symptoms. For example, > 50% of the TLVs and > 60% of the California acute RELs based their end points on irritation (Collins et al. 2004). However, human studies from which to develop acute exposure guidance are not available for many of the hundreds of substances of concern, and therefore reliance on animal studies is necessary. The RD50 test method is appealing because it generates data rapidly, requires minimal animal use, is low in cost, and is validated, calibrated, and standardized. The method was computerized, adding to the reproducibility of the results (Alarie 1998, 2000; Vijayaraghavan et al. 1994). The availability of RD50 in male mice for 89 chemicals (Schaper 1993), and their correlation with OELs suggests potential applicability to air exposure guidelines for the public. The result of this analysis quantitatively supports the applicability of RD50s in setting exposure guidelines for the public and workers.

We found a strong correlation between RD50 and human LOAELs, TLVs, and California RELs. Focusing on human studies where the subjects developed eye or respiratory irritation responses, we observed a strong correlation ($R^2 = 0.80$) between RD50s and LOAELs for 25 chemicals with irritating effects. The correlation remained close to 0.8 after conducting various subanalyses, indicating that the strains of mice or the RD50 exposure time does not substantially affect the correlation. Previously, Nielsen et al. (1995) proposed an indoor air guideline for the public between 0.025 and 0.25 times the OEL, similar to 0.0008 and 0.0008 times the RD50. In our analysis, the RD50 to REL correlation can be expressed as REL = 0.00026 × RD$^{1.4}$. Derived as follows:

$$\log_{10} \text{RD}_{50} = 0.71 \log_{10} \text{REL} + 2.55$$

$$10^{\log_{10} \text{RD}_{50}} = 10^{0.71 \log_{10} \text{REL} + 2.55}$$

$$\text{RD}_{50} = \text{REL}^{0.71} \times 10^{2.55}$$

$$\text{REL} = \text{RD}_{50}^{0.71} \times 10^{2.55}$$

$$\text{REL} = \text{RD}_{50}^{1.4} \times 10^{-3.59}$$

$$\text{REL} = 0.00026 \times \text{RD}_{50}^{1.4}$$

Exposure times in the human studies varied from 1 to 480 min, and a subanalysis looking specifically at the effect of the duration of exposure made no significant change to the correlation. Further, subanalyses using LOAELs more closely associated with either upper respiratory or lower respiratory effects did not make a significant change to the correlations. Although the variability in the response rate, interindividual sensitivity, and differences in human study design, as described in Table 1, would be expected to have reduced the correlation with the RD50, specific factors were...
not identified in our subanalyses. Thus, we conclude that the irritating symptoms in humans correlate well with the RD50 of animals irrespective of the specific acute exposure duration. These results not only support the use of the RD50 in setting guidelines for acutely irritating compounds, but also suggest that a concentration–time extrapolation for these effects appears unwarranted. This is consistent with the finding by Shusterman et al. (2006) that the human response to sensory irritants reached a plateau rapidly. Thus, the response appears to be influenced to a greater extent by the exposure concentration rather than the exposure time over the period of observation for most animal and human experiments considered in the present analysis, and over the periods of concern for the TLVs (15 min to 8 hr) and acute RELs (1 hr).

The results of this analysis are subject to several limitations. First, the number of available human studies limits the LOAEL data, and it is unlikely that human data will significantly increase in the future. The number of comparisons could increase as the numbers of RD50s increase for chemicals with human data. However, considering the robustness of the subanalyses, and the historical correlation of the RD50 to the TLV, a significant change in the RD50 to LOAEL correlation is unlikely after adding other sensory irritants in the analysis. Finally, we address issues raised by Bos et al. (1992, 2002, 2003).

First, Bos et al. (2003) claimed that the RD50–OEL correlation is expected because

Table 3. Summary of linear least-squares regression analyses for various comparisons.

| Description of analysis                                                                 | No. of compounds included | No. of data points included | Regression line                  | R² value |
|----------------------------------------------------------------------------------------|---------------------------|-----------------------------|----------------------------------|---------|
| All RD50s identified in all strains of mice vs. all human LOAELs identified (Figure 1) | 25                        | 198                         | logRD50 = 1.16(log LOAEL) + 0.77 | 0.82    |
| Evaluation using male mice and RELs set by OEHHA for airborne toxicants (Figure 2)    | 16                        | 37                          | logRD50 = 0.71(log REL) + 2.55   | 0.71    |
| Evaluation using male mice and the TLV (Figure 3)                                      | 24                        | 61                          | logRD50 = 0.86(log TLV) – 1.13   | 0.86    |
| Addressing issues of human LOAEL variabilities                                         |                           |                             |                                  |         |
| Evaluation using all RD50s identified in all strains of mice vs. the lowest human LOAEL for each compound | 25                        | 58                          | logRD50 = 1.13(log LOAEL) + 1.26 | 0.81    |
| Analysis for male mice log RD50 vs. log LOAEL using lowest RD50 values with the lowest LOAEL values | 25                        | 25                          | logRD50 = 1.01(log LOAEL) + 1.21 | 0.77    |
| Analysis for male mice log RD50 and human log LOAEL for lower respiratory end points    | 5                         | 29                          | logRD50 = 1.08(log LOAEL) + 1.21 | 0.58    |
| Analysis for male mice log RD50 and human log LOAEL for upper respiratory end points    | 23                        | 166                         | logRD50 = 1.22(log LOAEL) + 0.69 | 0.82    |
| Analysis for male mice log RD50 and human log LOAEL for higher quality human studies    | 7                         | 43                          | logRD50 = 1.40(log LOAEL) + 0.98 | 0.82    |
| Analysis for male mice log RD50 and human log LOAEL for human studies not selected as higher quality | 25                        | 155                         | logRD50 = 1.18(log LOAEL) + 0.73 | 0.79    |
| Evaluating influence of mouse strain                                                    |                           |                             |                                  |         |
| Evaluation using only Swiss-Webster mice and all human LOAEL values (Figure 2)         | 19                        | 75                          | logRD50 = 1.12(log LOAEL) + 0.93 | 0.74    |
| Evaluation using all non–Swiss-Webster mice and all human LOAEL values (Figure 3)     | 23                        | 120                         | logRD50 = 1.20(log LOAEL) + 0.73 | 0.83    |
| Evaluating changes in exposure duration                                                 |                           |                             |                                  |         |
| Evaluation using male mice and human LOAEL values from exposures of ≤ 10 min           | 16                        | 67                          | logRD50 = 1.27(log LOAEL) + 0.726 | 0.76    |
| Evaluation using male mice and human LOAEL values from exposures of > 10 min           | 18                        | 127                         | logRD50 = 1.11(log LOAEL) + 0.838 | 0.80    |
| Evaluation using male mice and human LOAEL values from exposures of ≥ 60 min           | 15                        | 101                         | logRD50 = 1.08(log LOAEL) + 0.89 | 0.80    |
| Log RD50 vs. log RD50 for RD50 values with time < 10 min                               | 16                        | 44                          | logRD50 = 1.04(log LOAEL) + 0.76 | 0.77    |
| Log RD50 vs. log RD50 for RD50 values with time > 10 min                               | 10                        | 43                          | logRD50 = 1.51(log LOAEL) + 0.56 | 0.87    |
| Log RD50 vs. log LOAEL for RD50 values with time equivalent to 10 min                  | 16                        | 111                         | logRD50 = 1.3(log LOAEL) + 0.78  | 0.80    |
| LogRD50 vs. log LOAEL for RD50 values at times not equivalent to 10 min                | 22                        | 86                          | logRD50 = 1.09(log LOAEL) + 0.77 | 0.8     |

OEHHA, Office of Environmental Health Hazard Assessment.
most OELs are based on animal data. Although many OELs are based on animal data, many are based on human data as well. Of the 24 substances we evaluated in our RD50–OEL correlation, the OEL for only one compound, n-pentyl acetate, relied on the RD50 for its derivation, which was based solely on animal data. The strong correlation between RD50s and human LOAELs also addresses this concern.

Second, Bos et al. (2002) reported the RD50 did not correlate well with histopathologic changes in the respiratory tract or with corrosivity, and therefore RD50 were inappropriate to evaluate respiratory tract irritation. However, the stated purpose of the ASTM standard is to evaluate sensory irritation potential, not histopathology or corrosivity. In our comparison of the RD50 with human irritation LOAELs, the correlation was strong with the inclusion of respiratory tract irritation end points in the analysis. Further, the risk assessment framework for occupational and public exposure levels addresses the concerns regarding the potential for other, more severe effects. In cases where other health effects occur at or below levels producing sensory irritation, exposure guidelines use the more sensitive adverse effect.

Third, Bos et al. (1992) raised concerns regarding the inconsistency of RD50 among strains and species. Although RD50 have been generated for various strains and species with varying test procedures, adhering to the ASTM standard method addresses this concern. Limiting the RD50 test to those conducted in mice, or Swiss-Webster mice, and limiting the exposure time keeps the test to a more standardized method, although intrastrain variability was not a cause for concern in our subanalyses. Finally, we addressed the concern regarding time–concentration response curves (Bos et al. 1992), with separate subanalyses based on exposure time. These analyses show that time did not appear to be a factor in our analyses. Our presumption is that if the study adheres adequately to the ASTM standard method, experimental exposure time plays a minor role. It is also worth pointing out that all of the figures comparing RD50 to LOAELs, RELs, and TLVs are plotted on a log–log plot because of the wide range of values. Because of the nature of log–log plots, the correlation is higher compared with the same correlation using a nonlogarithmic scale.

The applicability of the RD50 test to human health protection has been demonstrated in several analyses, but extrapolation of the test results to the general public would be improved with greater focus on the tail of the dose–response curve, to ensure protection of sensitive subpopulations. One solution would be for RD50 studies to report sufficient information to calculate a benchmark dose (BMD) value, and not focus solely on the specific RD50 value. A standardized BMD value could be calculated at the tail of the distribution, taking into account the slope of the dose–response curve. Alternatively, the test procedure could be refined to identify the “just detectable effect level,” which is approximately a 12% decrease in the respiratory rate (Alarie 1998). Although some work has been done in this area (Boylin et al. 1996), additional information is needed to better understand the tail of the dose–response curve and to address any concerns for spurious results from low exposure concentrations. The reported just detectable effect level of 12% appears to be close to the no observed effect level of the procedure. Use of this response rate in risk assessment is consistent with the recommendation by the U.S. EPA (2007) that the BMD for a continuous response may be set on statistical criteria of distinguishability from the control value, as well as on grounds of anticipated biological significance. A major benefit of focusing on the just detectable effect level would be to reduce potential animal suffering, and possibly animal usage.

In conclusion, the RD50 test is a good starting point for setting exposure standards for acute airborne irritants. As noted by Alarie et al. (2000), the TLV may need to be <0.03 RD50 to prevent other toxic effects. Consequently, the literature should be adequately evaluated to determine that sensory irritation is likely the most sensitive adverse effect. The application of RD50 appears most useful when qualitative data are available indicating sensory irritation as the most sensitive adverse effect, but quantitative human data are lacking. The RD50 has proven its usefulness with the ability to appropriately rank the potency of airborne chemicals as sensory irritants and help establish exposure limits. A strong correlation between RD50 and LOAELs provides further support for using RD50 in determining guidance levels to protect the general public from sensory irritants.
