Calculation of Rat Breathing Rate Based on Bodyweight

Office of Environmental Health Hazard Assessment
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Introduction

Rat breathing rate is a sensitive parameter in models used to characterize health risks, and predictive models of minute volume in rats are available in the peer-reviewed literature and in government reports. A comprehensive analysis of rat minute volume data has not been undertaken since 1988, and since that time, new methods to assess experimental animal breathing rates have been developed and implemented; these methods may more accurately reflect true resting rates of inhalation. Several programs within the Office of Environmental Health Hazard Assessment (OEHHA) use breathing rate equations to calculate doses from inhalation studies in rats based on the bodyweights of the animals studied. In an effort to refine and update the approach used to calculate rat breathing rates for use in dose response assessments, OEHHA:

- Reviewed the data used to derive the primary equations previously used by OEHHA programs
- Conducted a focused literature search for recent studies containing information on inhalation rates
- Identified the subset of high-quality study data (defined below) from literature search results and from the set of previously reviewed studies that best captures breathing rates of rats at rest
- Used the high-quality data subset to derive a new inhalation rate equation by fitting a model of the form

  $$I = a \times (bw)^{2/3} ,$$

  where *a* is a parameter to be estimated and *bw* represents bodyweight.

While the initial effort of the working group was limited to studies in rats, OEHHA anticipates conducting similar efforts to develop equations for calculating breathing rates for other species.

Review of previously used equations

There are two primary equations that have been used by OEHHA programs to calculate inhalation rates in rats. Anderson et al. (1983) derived the equation

$$I = 0.105 \times \left(\frac{bw}{0.113}\right)^{2/3} \quad \text{in m}^3\text{/day}$$

based on data from Guyton et al. (1947), which showed that rats with an average weight of 0.113 kg breathe 105 L/day (= 0.105 m^3/day). The US Environmental Protection Agency (US EPA 1988a and 1994) derived the equation $I = 0.80 \times bw^{0.8206}$ in m^3/day by fitting a linear model of the form $\ln IR = \beta_0 + \beta_1 \times \ln bw$ to data from several studies in rats, the most recent of which was published in 1986.

The working group identified several key limitations inherent in these equations:

- The Anderson et al. (1983) equation was informed by data from a single study
- Some of the data used for the US EPA (1988a and 1994) equation included transcription errors (e.g. duplicates, typographical errors)
- Both equations lack data from recent studies (i.e., studies conducted in the last 31 years)
- Some data used in the derivation of both equations come from studies which employed methods that are thought to alter normal physiological conditions, such as anesthetization, cannulation, and restraint.

In light of these issues, OEHHA concluded that a thorough examination of the data used to derive the Anderson et al. (1983) and US EPA (1988a and 1994) equations should be undertaken, and that a literature search should be conducted to identify any new studies.

Literature search

A literature search was conducted to identify recent studies reporting rat inhalation rates under normal physiological conditions. Searches were conducted in PubMed and in targeted journals, including Inhalation Toxicology, Journal of Applied Physiology, Journal of Physiology, Journal of Toxicology and Environmental Health, Respiration Physiology, Respiratory Physiology & Neurobiology, and Toxicological Sciences. Literature was identified using relevant search terms including “ventilation rates”, “minute volume”, “minute ventilation”, “inhalation rates”, and “rats”.

Selection of studies for new subset

An initial set of studies was compiled that included the studies in the US EPA 1988a (Blackburn) report, studies in the US EPA 1988b (Arms and Travis) report, and studies from the literature search described above. From the search results, a set of 250 articles published by December 2017 was retrieved for detailed review.

The working group determined that the highest quality data for analysis of rat inhalation rates would measure breathing in rats under as normal physiological conditions as possible. In order to be considered for inclusion, a study must have reported average body weight measured in temporal proximity to minute volume. High quality studies would include indicators that the animals were quiet and breathing evenly. The highest quality data would include adult animals from strains typical of toxicity studies. Adult animals were considered to be those approximately seven weeks of age or older. In the absence of reported age of animals, OEHHA decided to include the studies where the average bodyweight clearly indicates adulthood for that strain and gender. In consideration of these factors, most studies in which animals were very young or of strains not commonly used in toxicity testing or genetically modified to be pre-disposed for certain diseases were excluded, as were most studies in which animals were anesthetized during measurements and/or underwent tracheal cannulation prior to measurements. Prior anesthesia and prior surgical procedures were acceptable, so long as the procedures were minor and there was sufficient recovery time for animals prior to inhalation rate measurements. Generally, data from studies involving restrained animals were included only if the authors indicated that an acclimation period took place following restraint, or otherwise established stable ventilation. Other factors that may influence inhalation rates, such as room temperature, relative humidity, lighting conditions, and others, were not consistently reported across studies and consequently were not part of the criteria considered for inclusion in the high quality data subset.

The working group identified some studies that did not meet a strict application of the previous criteria, but were included where it could be established that the animals reached a reasonably normal physical condition for at least some measurements. For example, the working group decided to include data from Whitehead et al. (1999) in which animals were subjected to light anesthesia. Data from a study conducted by Olson and Dempsey (1978) were also included despite the fact that the animals underwent a cannulation procedure[1] because the authors stated that the animals had a two-week recovery period following cannulation before inhalation rate measurements were recorded. The working group evaluated 250 studies for inclusion using the criteria described previously. Ultimately, 49 studies were determined to contain data that met the selection criteria and 88 data points from these studies were used for modeling. Note that where studies included repeat measures on the same animals in close temporal proximity, a single data point was selected. Listed below are the final subset of studies included in this analysis:

[1] One to two weeks prior to initial control measures, rats were anesthetized and a chronically indwelling catheter was placed through the femoral artery of each rat into the abdominal aorta distal to the renal arteries and connected to an opening in the upper neck where the catheter was secured to an adhesive collar.

Bairam et al., 2009
Bavis et al., 2006
Chen et al., 1989
Colman and Miller, 2001
Cummings and Heitcamp, 1981
Cyphert et al., 2015
Cyphert et al., 2016
Donovan et al., 2011
Doperalski et al., 2008
Dye et al., 2015
Forster et al., 2003
Gamboa et al., 2003
Genest et al., 2004
Goineau et al., 2010
Gordon et al., 2010
Gordon et al., 2013
Guyton, 1947
Haouzi et al., 2009
Henderson et al., 2014
Hodges et al., 2013
Holley et al., 2012
Iiyori et al., 2003
Kuo et al., 2011
Lai et al., 1978
Leavens et al., 2006
Leong et al., 1964
Lin et al., 1983
Liu et al., 2011
Olson and Dempsey, 1978
Mantilla et al., 2011
Mauderly et al., 1979
Mauderly, 1986
Mautz and Bufalino, 1989
Pauluhn and Thiel, 2007
Polianski et al., 1984
Schlenker, 2016
Seifert and Mortola, 2002
Shore et al., 2000
Silva et al., 2017
Snow et al., 2017
Soulage et al., 2004
Strohl et al., 1997
Tsuji et al., 2011
Walker et al., 1985
Wenninger et al., 2006
Whitehead et al., 1999
Wiester et al., 1988
Xu et al., 2014
Young et al., 2013

<u>Model fitting</u>

The selected model, $I = a \times bw^{2/3}$, raises the animal body weight (in kilograms, kg) from the study in question to the 2/3 power (a commonly used allometric scaling ratio), and this quantity is multiplied by a constant informed by breathing rate data. The equation is set to intercept the origin (which is biologically appropriate when predicting inhalation rates based on body weight).

A weighted regression was used since the data being modeled in this analysis were means from samples of different sizes. In situations with aggregated data such as this, heterogeneous variance is expected, and applying weights allows the model fitting software to prioritize fit to data points with greater weights. When the variance associated with each data point is unknown (as in this case) and when heterogeneity is thought to arise from differences in sample sizes, a common approach is to base the weights on the sample sizes themselves. In this way, data points derived from studies with larger sample sizes, which are expected to have smaller variance, have greater weights than data points derived from studies with smaller sample sizes, which are expected to have larger variance. The weights used in this analysis were:

$$w_i = \frac{N \times T_i}{\sum T_i}$$

where N = number of data points and T_i = sample size for study *i*. This method ensures that the weights sum to N and studies with the same sample size have the same weight.

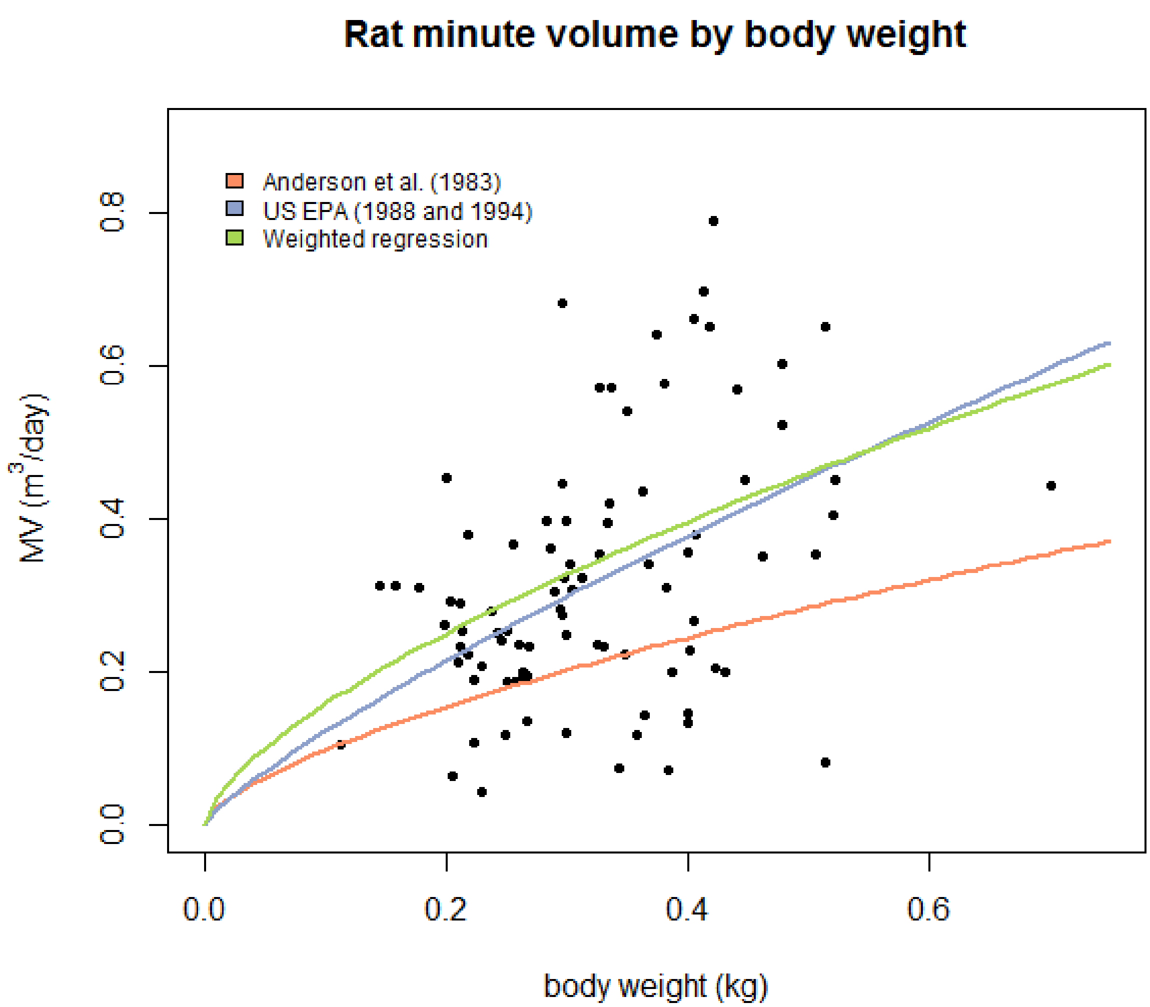
Analyses were performed in R (Version 3.4.2)[2]. The resulting weighted regression model equation was $I = 0.702 \times bw^{2/3}$ in unit of m^3/day and bodyweight in kg (adjusted $R^2 = 0.8347$; see later discussion regarding additional model diagnostics).

The plot below shows how the fit of the equation from the weighted regression compares to the fit of the equations from Anderson et al. (1983) and US EPA (1988a and 1994) to the observations from the high quality data subset. The weighted regression equation better fits the full dataset than Anderson et al. (1983), which was based on a single data point, and provides a similar fit to the US EPA equation. OEHHA will rely on the equation below, since it is based on a robust and up-to-date set of high quality data that has been quality checked for typographical error:

$$I = 0.702 \times bw^{2/3} \text{ in } m^3/\text{day}$$

[2]R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.R-project.org/.

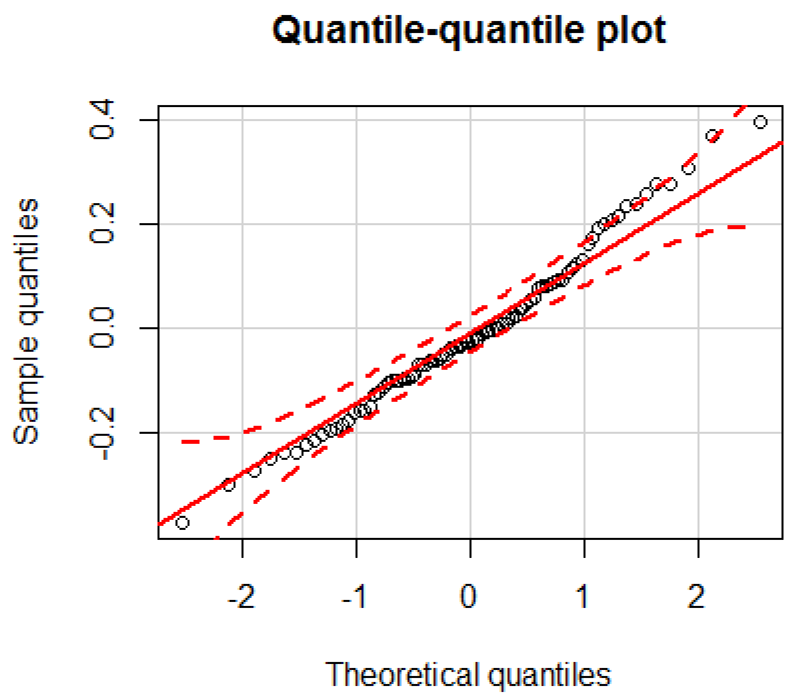
This equation will be used when it is necessary to calculate the breathing rate of rats in a study, based on their body weight, and when better information of breathing rate for the rats under test is not available.



Additional model diagnostics

As reported earlier, the weighted linear regression model described above generated an adjusted R^2 value of 0.8347, indicating that the model explains a substantial portion of the variation in the data, and the highly significant *p*-value for the F-statistic further supports this conclusion ($p < 0.0001$).

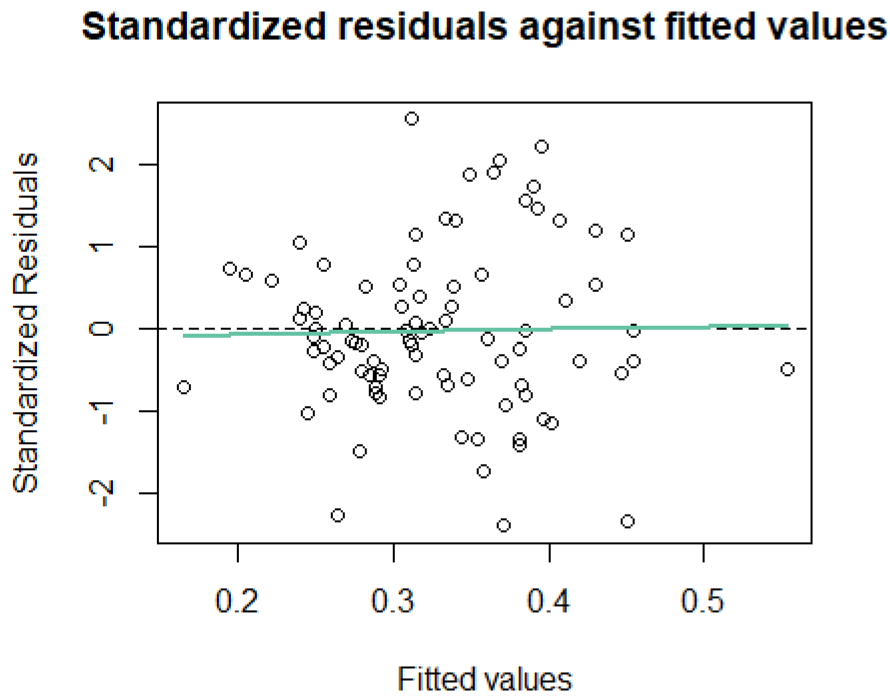
In assessing the overall suitability of the linear model and adequacy of fit, standard diagnostic plots were used to check the assumptions of normally distributed errors, independence of observations[3], linearity of relationship, and homogeneity of variance. To begin, the quantile-quantile plot of the residuals[4] below shows that the points follow the solid line fairly well, with a slight but progressive divergence from the true normal distribution in the right tail, shown by points located on or slightly outside the dashed 95% confidence bounds. Overall, the plot does not provide strong evidence against the assumption that the errors are normally distributed.



In the figure below showing the standardized residuals from the weighted regression plotted against the fitted values, the overlaid smoothing spline in teal helps to visualize the fact that the magnitude of the standardized residuals is not changing with the level of the fitted values in an appreciable pattern or in a manner that would suggest nonlinearity or dependence. Further, the relatively evenly scattered distribution of the values around y = 0 indicates that the variance of the observed data is consistent with the weights used. There are a couple of relatively large residuals but close examination of the individual study data does not point to any reason to classify the corresponding

[3] While many different studies from the literature are represented in the data used for this regression analysis, multiple values were reported and used from some studies (e.g. different rates for males and females, different rates for different strains of rat, etc.) so the independence of observations is not necessarily implied.
[4] Produced using the qqPlot() function in the 'car' package:
Fox J and Weisberg S (2011). An {R} Companion to Applied Regression, Second Edition. Thousand Oaks CA: Sage. Available from: http://socserv.socsci.mcmaster.ca/jfox/Books/Companion

observations as outliers and remove them from the analysis. Overall, the diagnositic plots indicate that the model fits the data adequately.



Data

Strain	Sex	BW (kg)	MV observed (L/min)	MV observed (m3/day)	Sample size	Reference
White rat	Not specified	0.113	0.073	0.105	35	Guyton (1947)
F344/Crl Lov	F	0.145	0.216	0.311	10	Mauderly (1986)
Brown Norway	M	0.158	0.217	0.312	10	Hodges et al. (2013)
Brown Norway	M	0.177	0.216	0.310	11	Hodges et al. (2013)
F344/Crl Lov	F	0.199	0.181	0.261	10	Mauderly (1986)
Sprague-Dawley	F	0.200	0.315	0.454	6	Xu et al. (2014)
Sprague-Dawley	M	0.203	0.202	0.291	6	Hodges et al. (2013)
Sprague-Dawley	F	0.206	0.043	0.062	8	Schlenker (2016)
Sprague-Dawley	M	0.210	0.148	0.213	15	Seifert and Mortola (2002)
Wistar	M	0.211	0.162	0.233	10	Leong et al. (1964)
Sprague-Dawley	M	0.212	0.201	0.289	6	Hodges et al. (2013)
Wistar	M	0.213	0.175	0.252	11	Colman and Miller (2001)
F344/Crl Lov	F	0.219	0.154	0.222	10	Mauderly (1986)
F344/Crl Lov	M	0.219	0.264	0.380	10	Mauderly (1986)
Sprague-Dawley	F	0.223	0.075	0.108	7	Holley et al. (2012)
Long-Evans	F	0.223	0.131	0.189	9	Whitehead et al. (1999)
Holzman	M	0.230	0.143	0.206	9	Gamboa et al. (2003)
Brown Norway (Mcw)	M&F	0.230	0.029	0.042	26	Forster et al. (2003)
Wistar	M&F	0.238	0.194	0.279	8	Pauluhn and Thiel (2007)
Sprague-Dawley	M	0.242	0.174	0.251	11	Cummings and Heitcamp (1981)
Fischer 344/N	F	0.246	0.167	0.240	5	Chen et al. (1989)
Brown Norway	M&F	0.250	0.081	0.117	21	Strohl et al. (1997)

Sprague-Dawley	F	0.251	0.175	0.252	11	Cummings and Heitcamp (1981)
Sprague-Dawley	F	0.251	0.130	0.187	8	Bavis et al. (2006)
F344/Crl Lov	F	0.255	0.254	0.366	10	Mauderly (1986)
Sprague-Dawley	M	0.258	0.129	0.186	8	Mautz and Bufalino (1989)
Sprague-Dawley	F	0.261	0.164	0.236	15	Genest et al. (2004)
Sprague-Dawley	M	0.264	0.139	0.193	16	Mautz and Bufalino (1989)
Sprague-Dawley	M	0.264	0.134	0.200	16	Mautz and Bufalino (1989)
Sprague-Dawley	F	0.267	0.134	0.134	7	Doperalski et al. (2008)
Sprague-Dawley	M	0.267	0.134	0.193	8	Mautz and Bufalino (1989)
CD IGS	F	0.269	0.162	0.233	16	Leavens et al. (2006)
Sprague-Dawley	M	0.284	0.276	0.397	8	Lai et al. (1978)
Sprague-Dawley	M	0.287	0.251	0.361	6	Young et al. (2013)
Sprague-Dawley	M	0.290	0.212	0.305	6	Young et al. (2013)
Sprague-Dawley	M	0.294	0.195	0.281	6	Young et al. (2013)
Sprague-Dawley	M	0.296	0.190	0.274	6	Polianski et al. (1984)
Brown Norway	M	0.296	0.473	0.681	12	Gordon et al. (2010)
F344	M	0.297	0.309	0.445	9	Wiester et al. (1988)
Wistar	M	0.299	0.225	0.324	10	Leong et al. (1964)
Wistar	M	0.300	0.172	0.248	6	Walker et al. (1985)
Not specified	NS	0.300	0.275	0.396	48	Lin et al. (1983)
Sprague-Dawley	M	0.300	0.083	0.120	4	Mantilla et al. (2011)
Sprague-Dawley	M	0.303	0.236	0.340	67	Olson and Dempsey (1978)
Sprague-Dawley	M	0.305	0.214	0.308	8	Lai et al. (1978)
Sprague Dawley	M&F	0.312	0.224	0.322	14	Shore et al. (2000)
Wistar	M	0.325	0.163	0.234	8	Silva et al. (2017)
Sprague-Dawley	M	0.328	0.246	0.354	6	Henderson et al. (2014)

Wistar (Kyoto)	M	0.328	0.397	0.572	8	Dye et al. (2015)
Sprague-Dawley	M	0.330	0.161	0.232	11	Iiyori et al. (2003)
Sprague-Dawley	M	0.334	0.274	0.395	6	Henderson et al. (2014)
F344/Crl Lov	M	0.336	0.292	0.420	10	Mauderly (1986)
Wistar Kyoto	M	0.337	0.398	0.573	8	Dye et al. (2015)
Brown Norway	M	0.343	0.052	0.074	6	Donovan et al. (2011)
Sprague-Dawley	M	0.349	0.154	0.222	6	Liu et al. (2011)
F344	M	0.350	0.375	0.540	24	Cyphert et al. (2015)
Sprague-Dawley	M	0.358	0.081	0.117	8	Schlenker (2016)
Wistar	M	0.363	0.303	0.436	18	Snow et al. (2017)
Sprague-Dawley	M&F	0.365	0.100	0.143	16	Strohl et al. (1997)
F344/Crl Lov	M	0.368	0.236	0.340	10	Mauderly (1986)
Brown Norway	M	0.375	0.445	0.641	12	Gordon et al. (2010)
F344	M	0.381	0.400	0.576	24	Cyphert et al. (2015)
Long Evans	M&F	0.383	0.215	0.310	10	Mauderly et al. (1979)
Sprague-Dawley (217)	Not Specified	0.384	0.050	0.072	16	Wenninger et al. (2006)
Sprague-Dawley	M	0.387	0.137	0.198	7	Holley et al. (2012)
Sprague-Dawley	M	0.400	0.248	0.357	25	Genest et al. (2004)
Wistar (Han)	M	0.400	0.092	0.132	8	Goineau et al. (2010)
Wistar (Han)	M	0.400	0.101	0.145	8	Goineau et al. (2010)
Fischer 344/N	M	0.402	0.159	0.228	5	Chen et al. (1989)
Sprague-Dawley	M	0.406	0.184	0.265	11	Bavis et al. (2006)
Wistar	M	0.406	0.459	0.661	8	Dye et al. (2015)
F344/Crl Lov	M	0.407	0.264	0.380	10	Mauderly (1986)
Wistar	M	0.414	0.484	0.698	8	Dye et al. (2015)
Sprague-Dawley	M	0.419	0.452	0.651	8	Dye et al. (2015)

Sprague-Dawley	M	0.422	0.549	0.790	8	Dye et al. (2015)
Sprague-Dawley	M	0.424	0.141	0.204	8	Kuo et al. (2011)
Sprague-Dawley	M	0.432	0.200	0.200	8	Doperalski et al. (2008)
F344	M	0.441	0.396	0.570	16	Cyphert et al. (2015)
F344	M	0.447	0.313	0.451	18	Cyphert et al. (2015)
Sprague-Dawley	M	0.462	0.243	0.350	8	Tsuji et al. (2011)
Brown Norway	M	0.479	0.419	0.524	8	Cyphert et al. (2016)
F344	M	0.479	0.364	0.603	12	Gordon et al. (2010)
Sprague-Dawley	M	0.507	0.245	0.353	8	Tsuji et al. (2011)
Brown Norway	M	0.514	0.453	0.081	10	Donovan et al. (2011)
Sprague-Dawley	M	0.514	0.056	0.652	8	Gordon et al. (2013)
Sprague-Dawley	M	0.521	0.282	0.406	15	Bairam et al. (2009)
Wistar	M	0.522	0.313	0.451	10	Soulage et al. (2004)
Sprague-Dawley	M	0.701	0.308	0.444	5	Haouzi et al. (2009)

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