AFRL-RH-WP-TR-2020-0013

Effect of Exertion on Adult Breathing Parameters: Literature Review and Meta-analysis

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March 5, 2020

Final Report

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REPORT DOCUMENTATION PAGE					*Form Approved OMB No. 0704-0188*
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1. REPORT DATE ***(DD-MM-YYYY)*** 05-03-2020			**2. REPORT TYPE** FINAL TECHNICAL		**3. DATES COVERED** ***(From – To)*** Jun 2019 – Mar 2020
4. TITLE AND SUBTITLE Effect of Exertion on Adult Breathing Parameters: Literature Review and Meta-analysis					**5a. CONTRACT NUMBER** 47QFWA18P0016
					5b. GRANT NUMBER
					5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) Lisa M. Sweeney, PhD					**5d. PROJECT NUMBER**
					5e. TASK NUMBER ID07180038
					5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Air Force Research Lab (AFRL) 711/HPW/RHM 2510 Fifth St., Bldg. 840 Wright-Patterson AFB, OH 45433-7913					**8. PERFORMING ORGANIZATION REPORT NUMBER** AFRL-RH-WP-TR-2020-0013
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)					**10. SPONSORING/MONITOR'S ACRONYM(S)**
					11. SPONSOR/MONITOR'S REPORT NUMBER(S)
12. DISTRIBUTION / AVAILABILITY STATEMENT DISTRIBUTION STATEMENT A. Approved for public release. Distribution is unlimited.					
13. SUPPLEMENTARY NOTES Cleared, 88PA, Case # 88ABW-2020-1029, 24 Mar 2020					
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15. SUBJECT TERMS Physiologically based pharmacokinetic modeling, inhalation, chemicals, exertion, cumulative risk assessment					
16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** Matthew W. Linakis, PhD
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	SAR	30	**19b. TELEPHONE NUMBER** ***(include area code)*** 937-713-0159

Standard Form 298 (Rev. 8-98)
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1.0 SUMMARY/ABSTRACT

The inhalation route is of particular concern for exposure to hazardous chemicals in the workplace and an important pathway for environmental exposures in everyday life. Physiologically based pharmacokinetic (PBPK) models have been proposed as tools for computation of internal dosimetry for both aggregate risk and cumulative risk. Among the stressors that are known to have an impact on the absorption, distribution, and elimination of chemicals are heat and exercise stress. The impact of these stressors on parameters used to describe inhalation was evaluated via literature review and synthesis. Data from up to 13 groups of healthy adult subjects were used to derive linear or second order polynomial relationships between exertion or heart rate and pulmonary ventilation rate, tidal volume, and breathing frequency. These relationships will allow future application of PBPK modeling-based strategies to prioritize among various cumulative risk scenarios involving chemicals and the many other stressors present in the workplace and other environments.

2.0 INTRODUCTION/BACKGROUND

The inhalation route is of particular concern for exposure to hazardous chemicals in the workplace (Lentz et al. 2015) and an important pathway for environmental exposures in everyday life. Within the Air Force Total Exposure Health framework (Korpe 2016), physiologically based pharmacokinetic (PBPK) models have been proposed as tools for computation of internal dosimetry for both aggregate risk (same chemical, multiple pathways) and cumulative risk (combined exposure to multiple chemicals and/or other stressors) (Sweeney et al. 2020). Among the stressors that are known to have an impact on the absorption, distribution, and elimination of chemicals are heat and exercise stress (Sidhu et al. 2011). Sidhu et al. (2011) previously reviewed the literature for the effects of heat and exertion on physiological parameters pertinent to PBPK models for drugs (e.g., cardiac output, regional distribution of blood flow). They integrated their findings across studies and across these two stressors by relating changes in other physiological parameters to changes in the heart rate. Their study, however, did not address the impact of these stressors on parameters that characterize breathing, as it was apparently not considered an important pathway for absorption or elimination for drugs.

In this investigation, the approach used by Sidhu et al. (2011) was extended to endpoints pertinent to describing breathing in PBPK models, specifically the pulmonary ventilation rate (volume/time), tidal volume, and breathing frequency. The limited data on inspiration and expiration times that were identified were also reported. These data will inform the adaptation of PBPK models developed for individuals "at rest" to provide predictions of dosimetry for inhalation exposures during exertion (or in a hot environment), similar to the case study provided by Sweeney et al. (2020).

3.0 METHODS

3.1 Literature Search and Study Selection

Relevant studies were identified by key word searches in PubMed (https://pubmed.ncbi.nlm.nih.gov/) as of June 25, 2019. Key words "human" and "heat or exertion or exercise" were included for all outcomes of interest. Candidate studies were prioritized for review using SWIFT-Review (Sciome, Inc., Version 1.42). Inclusion criteria were based in part on the problem formulation for air crew health risk assessment (Sweeney et al. 2020) as follows:

Population: healthy adults (age 18-65 years), male or female, of any ethnicity.

Exposure: acute exposure to heat or exertion; multiple levels of effort and quantification of level of effort preferred but not required

Comparator: physiological parameter values at normothermic room temperature, at rest

Outcome: primary interest—ventilation rate (key words: "ventilation rate" or "minute volume"; secondary interest—key words "tidal volume" and "breathing frequency". Information on breath duration (the inverse of breathing frequency), inhalation duration, exhalation duration, inspiratory duty cycle (inhalation duration/breath duration) were also outcomes of interest for data extraction, but were not the subject of key word searches.

Literature review and data extraction were discontinued when the author deemed that additional data sets were unlikely to change the central tendency predictions for pulmonary ventilation, the primary parameter of interest substantially (see section 4.2 for additional detail).

3.2 Data Extraction and Processing

Details describing the study subjects and study design were collected based on review of the papers and publically available supplementary materials, if applicable. Descriptors of interest for the study subjects were numbers of men and women, age (central tendency, range, variability), health status, potentially relevant professions or hobbies (e.g., athletic training), body mass index (BMI) (or height and weight), geographic residence, ethnicity, and known or potential overlap of participants across studies. Study design information of interest included posture, timing of measurements, the nature of the activity or exposure conditions, and the time course of activities (e.g., constant level of effort, step wise or continuously ramped increase in effort).

When available, physiological parameter values and levels of exertion were extracted from the text and tables. For data available only in graphical formats, WebPlotDigitizer, version 4.1 (https://apps.automeris.io/wpd/) was used to convert these data back to numerical form. Where data variability was reported as the standard error of the mean (SEM), this metric was converted to the standard deviation (SD) using the formula SD = SEM × square root of n (n = number of measurements). Where BMI data were not reported, BMI was calculated if height and weight information were available (BMI = weight/height^2, with weight in kg and height in m, or converted to those units). When individual height and weight data were reported, BMI was calculated for each individual, and the resulting individual BMI values were averaged. In the absence of individually reported data, an approximate central tendency BMI was calculated from the central tendency values of weight and height. The central tendency may refer to the mean, median, or midpoint of a range.

3.3 Data Synthesis and Reporting

Data collected during exposure to a stressor (exercise or heat) were normalized to (divided by) baseline values collected while the subjects were at rest in a normothermic environment. Meta-analyses were conducted for the outcomes of pulmonary ventilation, tidal volume, and breathing frequency, with regressions vs. level of exertion (work in W) and heart rate (in beats per minute). The exercise-related outcomes of two studies published by Quon et al. (2015 and 2016) were observed to be similar and were based on overlapping pools of subjects. The smaller (n = 19 participants) Quon et al. (2015) study was included in the meta-analysis rather than the larger (n = 25) Quon et al. (2016) study because Quon et al. (2015) reported heart rate data, while Quon et al. (2016) did not. The development of regression analyses of ventilatory parameters as a function of heart rate was a key objective of this analysis, in keeping with the approach used in Sidhu et al. 2011 for effects of exertion or heat on other physiological parameters, so this criterion superseded the possible preference for larger numbers of study subjects. Regressions were conducted in Excel using the polynomial or linear trendline option. In analyses of normalized physiological parameter values vs. work, the regression line was forced through an intercept of 1 for work = 0. Because studies had varying baseline heart rates, regressions with heart rate as the independent variable were not forced through “1” at a particular value for heart rate.

Data visualization incorporated distinctive symbols for the data sets to facilitate identification of possible outliers and for pattern recognition. Studies with gray symbols had a majority of female subjects, and studies with black symbols had a majority of male subjects. Where a single publication had multiple groups (e.g., men vs. women) or experimental conditions (e.g., upper body vs. lower body exercise), similar symbols are used.

Data were reported as mean ± SD (if available) or the mean alone, unless otherwise specified.

4.0 RESULTS

4.1 Selected Studies

Studies selected for the analysis were summarized in Table 1. Most of the studies involved a gradual increase in workload (either ramped or incremental) that averaged out to increases of 8-20 W per min., up to symptom-limited exhaustion. The design of the Vai et al. (1988) differs substantially in having levels of effort (which differ by 50 W) in a random order, and each level of effort is maintained for 30 seconds. Three of the test groups have some subjects near or exceeding the age limit specified in the problem statement (older subset in Faisal et al. 2015, Kurtobi et al. 1997, and Soumagne et al. 2016). Of these three groups of older adults, BMI was reported for two (Faisal et al. 2015 and Soumagne et al. 2016), and in both cases, the mean BMI (in kg/m^2) corresponds to the overweight range ($25 \leq BMI < 30$). The inclusion of these studies was initially considered provisional; inspection of the results and comparison to other studies does not suggest that they are outliers relative to other studies, so they were retained for the meta-analyses.

Table 1. Sources of Data for the Effect of Exertion on Pulmonary Ventilation Rate and Related Parameters

Reference	n[a]	% male	Age (CT)	BMI (CT)	Location	Mode of Exercise	Design	Other
Amman et al. 2010	5	100%	23.9	22.8	US	Cycle ergometer (legs)	Rest, then 3 min. each at 50, 100, and 150 W, followed by 4 minutes at 80% of peak capacity (~325 W) with no breaks	Subjects were moderately trained cyclists
						Arm cycling	Rest, then 25, 50, and 75 W for 3 minutes per interval with no rest between the 25 and 50 W interval and a 3 minute rest prior to the 75 W interval.	
Artal et al. 1986	39	0%	28.2	NR	US	Treadmill, constant speed	For mild or moderate exercise, constant pace and grade were maintained for 15 min. Strenuous effort at constant speed and increasing gradient was symptom limited.	Ventilation rate was computed by the current analyst from breathing frequency and tidal volume
Chetta et al. 2004	10	30%	33 (range: 25-49)	21	Italy	Walk test	Subjects performed two 6-min. symptom limited walk tests; only the second results were used.	Exertion was not described in terms of workload, but ventilation parameters could be correlated with paired heart rate data
Dorneles et al. 2019	10	20%	37.2	22.9	Brazil	Cycle ergometer	5 min. rest followed by 2 min. unloaded pedaling; workload	Subjects were the matched control group in a study of pulmonary ventilatory response to

Reference	n[a]	% male	Age (CT)	BMI (CT)	Location	Mode of Exercise	Design	Other
							was increased 15-20 W/min. until exhaustion	exercise in pulmonary arterial hypertension
Faisal et al. 2015	12	100	27 (range: 20-39)	24.8	Canada	Cycle ergometer	Stepwise incremental (25 W/3 min) exercise test up to peak exercise (symptom limited).	These study participants were the younger group in a study of the impact of age on respiratory function during incremental exercise.
	12	100	65 (range: 55-79)	26.7	Canada	Cycle ergometer	Stepwise incremental (20 W/2 min) exercise test up to peak exercise (symptom limited).	These study participants were the older group in the same study noted above.
Kilbride et al. 2003	14	100%	23.3	24.2	Ireland	Cycle ergometer	5-min. rest period followed by a 4-min. warm up at 20 W then 20 W/min increase in load to peak V_{O2} or subject was unable to continue.	Average weight of 82.1 kg
	10	0%	23.8	22.6	Ireland	Cycle ergometer	Same as above for men, but rate of workload increase was 15 W/min	Average weight of 63.4 kg; women had normal menstrual cycles and were tested during the mid-follicular stage
Kurtobi et al. 1997	10	100%	54 (range: 43-73)	NR	Japan	Seated upright on a cycle ergometer	After 5 min. rest and 1 min. unloaded pedaling, the load was incrementally increased by 2 W/6 seconds	Study subjects were the controls in a study of chronic heart failure

Reference	n[a]	% male	Age (CT)	BMI (CT)	Location	Mode of Exercise	Design	Other
Quon et al. 2015	19	63%	30	24	Canada	Cycle ergometer	Incremental exercise with stepwise increases of 20 W every 2 min. until maximum workload was achieved	Study subjects were the matched controls in a study of cardiorespiratory response to exercise in adults with mild cystic fibrosis. In the study as a whole (controls and subjects with cystic fibrosis), two participants were not Caucasian. Some participants participated in both this study and Quon et al. 2016.
Quon et al. 2016	25	68%	31	24	Canada	Cycle ergometer	Same as Quon et al. 2015	Study subjects were the controls in a study of exertional dyspnea in adults with cystic fibrosis. Some participants participated in both this study and Quon et al. 2015.
Soumagne et al. 2016	20	85%	60.7	26.6	France	Cycle ergometer	3-min. warm up followed by incremental, stepwise increases of 20 W per min. up to peak exercise (8-12 min.)	Study subjects (healthy, 55% smokers, average of 17.7 pack-years of tobacco) were the controls in a study of chronic obstructive pulmonary disorder and exercise tolerance
Takano 1988	12	0%	Range: 21-24	21.4	Japan	Mechanically braked cycle ergometer	Workload was increased by 15 W/min up to exhaustion	Trials were completed at 30 and 60 rpm.
Vai et al. 1988	4	100%	28	NR	France	Ergometric bicycle	30 sec. per work level at 50, 100, 150 or 200 W in random order	--

Reference	n[a]	% male	Age (CT)	BMI (CT)	Location	Mode of Exercise	Design	Other
Walsted et al. 2018	6	17%	30	24.7	England	Cycle ergometer	Incremental exercise test, 20 W/min	Study subjects were the controls in a study of exercise-induced laryngeal obstruction

[a] n = number of study subjects; CT = central tendency; NR = not reported

4.2 Pulmonary Ventilation Rate

Individual study data on pulmonary ventilation rate and heart rate are summarized in Appendix A, Table A-1 and Table A-2, respectively. The mathematical relationship between exertion (work) and ventilation rate was derived using all of the data, but the data are presented in two figure panels (with the common trendline) for improved visibility (Figure 1). A trendline with the Vai et al. (1988) data omitted yielded a modestly improved r^2 (0.847), but predicted ventilation ratios differed from line derived from the full data set by no more than 7.7% (fit not shown; $y = 1 + 0.0253 \times \text{work} + 2.24 \times 10^{-5} \times \text{work}^2$). Data to describe the relationship between heart rate and pulmonary ventilation rate changes were available for eight data series with seven groups of people in six published studies (Figure 2).

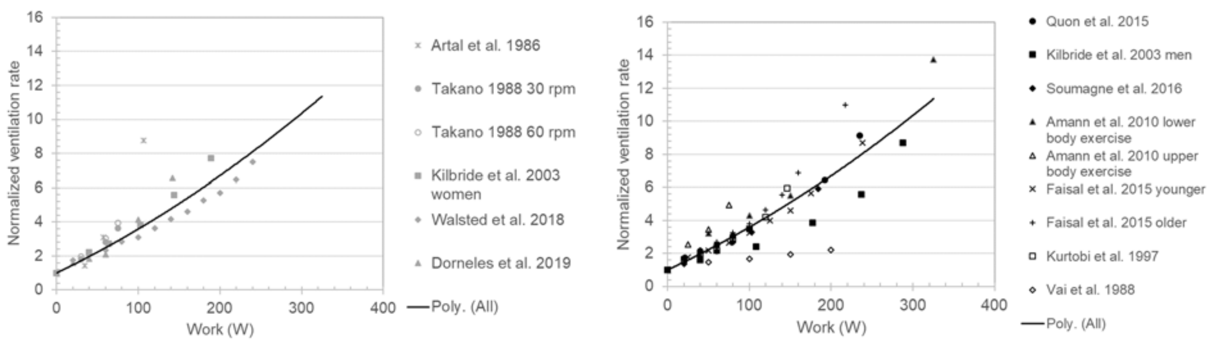


Figure 1. Change in pulmonary ventilation rate due to exertion: ventilation vs. work. (Left) Majority female studies. (Right) Majority male studies. The polynomial trendline describes the ratio of pulmonary ventilation during work (in W) to the rate at rest and was derived using all the data in both figures. $Y = 1 + 0.0232 \times \text{work} + 2.68 \times 10^{-5} \times \text{work}^2$ ($r^2 = 0.787$, n = 99 ventilation ratios, 15 series, work = 20 - 325 W).

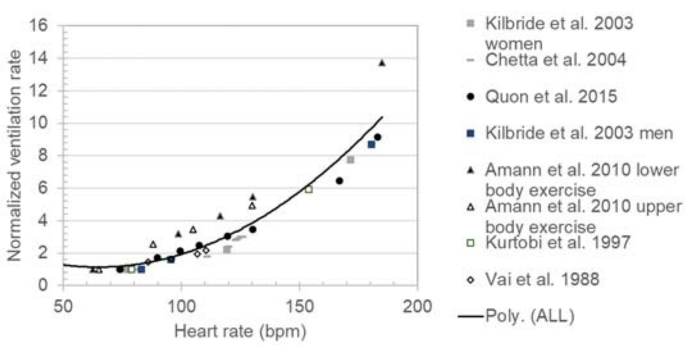


Figure 2. Change in pulmonary ventilation rate due to exertion: ventilation vs. heart rate. $Y = 3.82 - 0.0829 \times HR + 6.40 \times 10^{-4} \times HR^2$ ($r^2 = 0.895$, n = 37 ventilation ratios, 8 series, HR = heart rate of 62-185 beats per minute).

4.3 Tidal Volume

Individual study data on tidal volume are summarized in Appendix A, Table A-3. Similar to the presentation of the pulmonary ventilation rate data, the mathematical relationship between exertion (work) and tidal volume was derived using all of the data, but the data are presented in two figure panels (with the common trendline) for improved visibility (Figure 3). One notable contrast between the pulmonary ventilation vs. tidal volume data is that while the pulmonary ventilation rate data had a positive quadratic term, the tidal volume data had a negative one.

Likewise, data to describe the relationship between heart rate and tidal volume changes were available for the same data series used for the pulmonary ventilation rate analysis (Figure 4). Again, the correlation coefficient of heart rate with tidal volume is higher than the correlation of work and tidal volume.

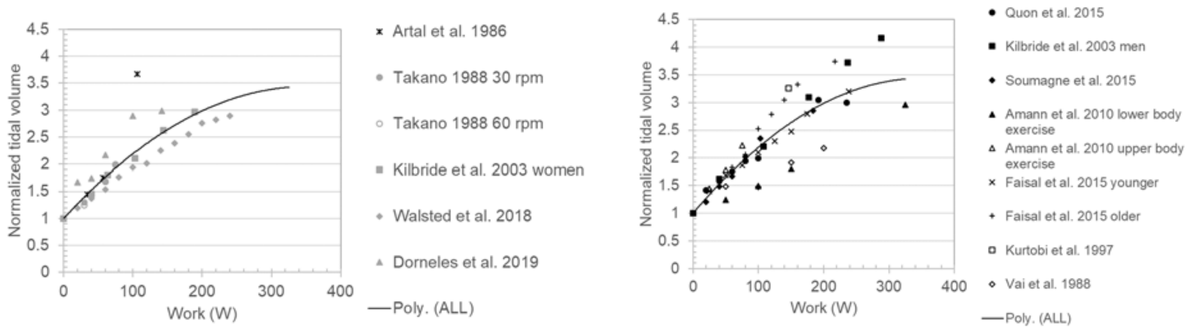


Figure 3. Change in tidal volume due to exertion: tidal volume vs. work. (Left) Majority female studies. (Right) Majority male studies. The polynomial trendline describes the ratio of tidal volume during work (in W) to the rate at rest and was derived using all the data in both figures. $Y = 1 + 0.0139 \times work + 1.98 \times 10^{-5} \times work^2$ ($r^2 = 0.813$, n = 99 tidal volume ratios, 15 series, work = 20 - 325 W).

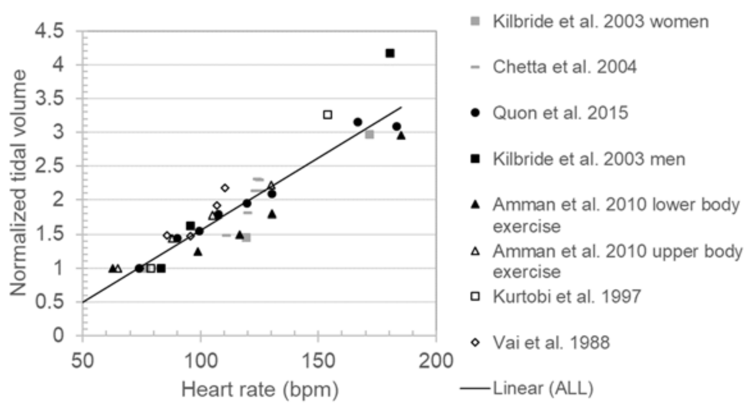
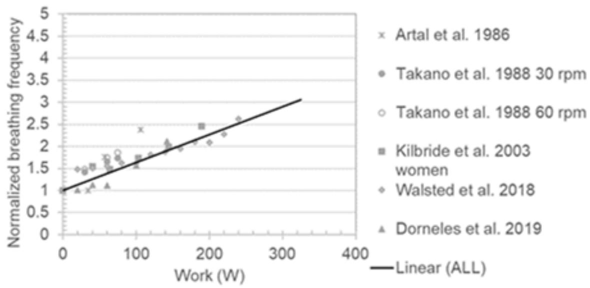


Figure 4. Change in tidal volume due to exertion: tidal volume vs. heart rate. $Y = -0.568 + 0.0216 \times HR$ ($r^2 = 0.862$, n = 37 tidal volume ratios, 8 series, HR = heart rate of 62-185 beats per minute).

4.4 Breathing Frequency

Individual study data on breathing frequency are summarized in Appendix A, Table A-4. As with the preceding presentations of the pulmonary ventilation rate and tidal volume data, relationships between breathing frequency and work (Figure 5) and heart rate (Figure 6) were derived by regression analyses. The correlations of breathing frequency with both work and heart rate were lower than the correlations obtained for pulmonary ventilation and tidal volume.



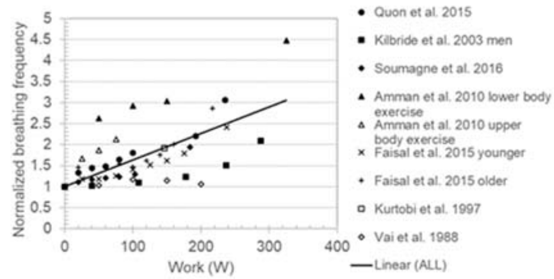


Figure 5. Change in breathing frequency due to exertion: breathing frequency vs. work. (Left) Majority female studies. (Right) Majority male studies. The polynomial trendline describes the ratio of tidal volume during work (in W) to the rate at rest and was derived using all the data in both figures. Y = 1 +0.00633 × work (r^2 = 0.510, n = 99 breathing frequency ratios, 15 series, work = 20 - 325 W).

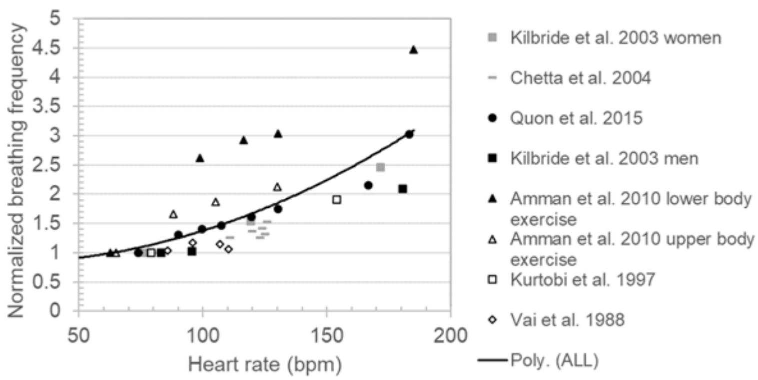


Figure 6. Change in breathing frequency due to exertion: breathing frequency vs. heart rate. Y = 0.855 - 0.00287 × HR+ 8.08 × 10^{-5} × HR^2 (r^2 = 0.556, n = 37 breathing frequency ratios, 8 series, HR = heart rate of 62-185 beats per minute).

4.5 Additional Breathing Cycle Parameters

Breathing cycle parameters other than breathing frequency were not the subject of targeted searches under this effort. In three studies that were used as sources of data on the key parameters of interest (see sections 4.2, 4.3, and 4.4), data were reported on inspiratory duty fraction (Chetta et al., 2004; Walsted et al. 2018) or both inspiration time and exhalation time (Takano 1988), which can be used to calculated the inspiratory duty fraction. These compiled data were reported in Appendix A, Table A-5 and A-6. The baseline values of inspiratory duty fraction were consistent among the studies (~33 to 44% of breathing time devoted to inhalation). The studies also consistently found small increases in the inspiratory duty fraction during exertion, but these increases were generally small (< 24%) and no correlation between exertion level and increase in the inspiratory duty fraction was evident in these limited data.

5.0 DISCUSSION

The studies used to derive relationships between exertion (or heart rate) and ventilation parameters cover age and gender reasonably well (Table 1). The lower and upper ends of the age range are represented among the 14 groups of subjects, though studies with central tendency ages in the middle of the range are lacking—no study group had a central tendency age between 37 and 54 years. The study groups include three that were 100% female, three that were majority female, two that were majority male and six that were 100% male. The publications generally did not explicitly report ethnicity. The geographical locations of the studies were predominantly in North America and Europe, plus two studies in Japan and one in Brazil.

Pulmonary ventilation rate changes were well described by a second order polynomial relationship between the level of exertion or heart rate and the ratio of pulmonary ventilation during work to the baseline rate (at rest) (Figure 1 and Figure 2). The correlation was better when heart rate was used as the basis, rather than work (in W). The data of Vai et al. (1988) appear to stray from the Figure 1 trendline more than any other pulmonary ventilation data set, perhaps due in part to study design differences (30 sec per level of effort, rather than a more sustained effort). By contrast, in Figure 2, the Vai et al. (1988) data were closer to the central tendency among the multiple studies, indicating that the instantaneous heart rate is a more sensitive indicator of physical stress than the work rate, which does not consider cumulative effects of sustained vs. brief exertion. Similar observations regarding the Vai et al. (1988) data apply to the tidal volume data (Figures 3 and 4) and breathing rate data (Figures 5 and 6), but to a lesser degree. Among the breathing frequency data sets, the Amman et al. (2010) lower body exercise data deviate the most from the trendlines (Figure 5 and 6); this data series has the lowest baseline breathing frequency, which may have contributed to abnormally high computed work-to-baseline ratios.

6.0 CONCLUSION

Sidhu et al. (2011) have previously described the relationship between heat or exertion, as manifested by increased heart rate, and changes in cardiac output and blood flow distribution, and applied this information in PBPK models of the disposition of drugs. To extend similar analyses to inhaled compounds, data were sought to develop similar relationships for key parameters used to describe pulmonary ventilation, tidal volume, and breathing frequency. A collection of 15 data sets from 13 groups of volunteers were used to derive mathematical relationships between exertion (described as “work”) and pulmonary ventilation, tidal volume and breathing frequency; eight data series from seven groups of volunteers were used to derive relationships between heart rate and the same three endpoints. These relationships will allow future application of PBPK modeling-based strategies (Sweeney et al. 2020) to prioritize among various cumulative risk scenarios involving chemicals and the many other stressors present in the workplace and other environments.

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APPENDIX A

Physiological Parameter Values

Table A-1. Effect of Exercise Stress on Pulmonary Ventilation Rate

Reference	Baseline Value (L/min) (n)	Stressor Description	Percentage of Baseline	Notes
Artal et al. 1986	9.34 (39)	34 W	143% (n = 15)	Central tendency estimated from mean tidal volume × mean breathing frequency
		57 W	309% (n = 14)	
		106 W	876% (n = 10)	
Kilbride et al. 2003 women	0.15 ± 0.03 L/min/kg (10) (~9.51 L/min)	40 W	220%	None
		64 W	272%	
		103 W	383%	
		144 W	557%	
		189 ± 11 W	773%	
Takano 1988 30 rpm	7.74 (rest) (12) 11.4 (0 W) (12)	30 W	181%	0 W conditions were described as “unloaded cycling”; 30-75 W outcomes were normalized to “rest” values rather than the 0 W values
		60 W	280%	
		75 W	362%	
Takano 1988 60 rpm	7.94 (rest) (12) 13.2 (0 W) (12)	30 W	197%	
		60 W	304%	
		75 W	394%	
Walsted et al. 2018	12.4 (rest) (6) 20.6 (0 W) (6)	20 W	176%	0 W conditions were not described; outcomes for non-zero work rates were normalized to the “rest” values rather than the 0 W values
		40 W	206%	
		60 W	235%	
		80 W	285%	
		100 W	311%	
		120 W	364%	
		140 W	417%	
		160 W	459%	
		180 W	525% (4)	
		200 W	572% (4)	
		220 W	647% (4)	
		240 W	750% (4)	
Dorneles et al. 2019	8.79 (10)	20 W	159%	None
		40 W	183%	
		60 W	210%	
		100 W	413%	
		142 ± 35 W	656%	
	10 ± 3 (10)	1 min.	180%	

Reference	Baseline Value (L/min) (n)	Stressor Description	Percentage of Baseline	Notes
Chetta et al. 2004	(5 min. baseline)	2 min.	240%	Changes during 6 min. walk test
		3 min.	280%	
		4 min.	290%	
		5 min.	300%	
		6 min.	300%	
Quon et al. 2015	13.7 (19)	20 W	171%	None
		40 W	212%	
		60 W	250%	
		80 W	304%	
		100W	345%	
		192 W	644%	
		235 W	915%	
Quon et al. 2016	13.0 (25)	20 W	177%	Not used for trendline development
		40 W	222%	
		60 W	257%	
		80 W	304%	
		100W	352%	
		196 W	685%	
		237 W	954%	
Soumagne et al. 2016	13.8 (20)	20 W	137%	None
		40 W	177%	
		60 W	214%	
		80 W	267%	
		103 W	327%	
		184 W	590%	
Kurtobi et al. 1997	10.2 ± 1.9 (10)	20 W	162%	None
		40 W	183%	
		60 W	217%	
		80 W	283%	
		100 W	348%	
		120 W	420%	
		146 ± 9 W	593%	
Faisal et al. 2015 older	11.5 ± 3.0 (12)	20 W	176%	None
		40 W	221%	
		60 W	269%	
		80 W	325%	
		100 W	379%	
		120 W	464%	
		140 W	554%	
		160 W	687%	
		217 ± 42 W	1097%	
		25 W	175%	None

Reference	Baseline Value (L/min) (n)	Stressor Description	Percentage of Baseline	Notes
Faisal et al. 2015 younger	12.7 ± 3.0 (12)	50 W	218%	
		75 W	264%	
		100 W	326%	
		125 W	399%	
		150 W	458%	
		175 W	563%	
		238± 48 W	871%	
Amann et al. 2010	10.9 ± 4.5 (5)	50 W	320%	Lower body exercise
		100 W	431%	
		150 W	549%	
		325 W	1373%	
	13 ± 4.5 (5)	25 W	254%	Upper body exercise
		50 W	346%	
		75 W	492%	
Kilbride et al. 2003 men	0.17 ± 0.04 L/min/kg (14) (~14.0 L/min)	40 W	159%	None
		108 W	240%	
		178 W	385%	
		237 W	557%	
		288 W	871%	
Vai et al. 1988	12.1 ± 1.6 (4)	50 W	145%	None
		100 W	165%	
		150 W	195%	
		200 W	219%	

Table A-2. Effect of Exercise Stress on Heart Rate

Reference	Baseline Value (beats per minute; bpm) (n)	Stressor Description	Rate (bpm)	Notes
Kilbride et al. 2003 women	77 ± 4 (10)	40 W	119 ± 17	None
		189 ± 11 W	172± 13	
Chetta et al. 2004	82 ± 10 (10) (5 min. baseline)	1 min.	111 ± 15	Changes during 6 min. walk test
		2 min.	120 ± 13	
		3 min.	123 ± 12	
		4 min.	124 ± 13	
		5 min.	125 ± 14	
		6 min.	126 ± 13	
Quon et al. 2015	74 (19)	20 W	90	None
		40 W	99	
		60 W	107	

Reference	Baseline Value (beats per minute; bpm) (n)	Stressor Description	Rate (bpm)	Notes
		80 W	120	
		100W	130	
		192 W	167 ± 13	
		235 W	183 ± 9	
Kurtobi et al. 1997	79 ± 6 (10)	146 ± 9 W	154 ± 16	None
Amann et al. 2010	63 ± 1 (5)	50 W	99 ± 4	Lower body exercise
		100 W	116 ± 3	
		150 W	130 ± 10	
		325 W	185 ± 5	
	65 ± 7 (5)	25 W	88 ± 9	Upper body exercise
		50 W	105 ± 13	
		75 W	130 ± 16	
Kilbride et al. 2003 men	83 ± 10 (14)	40 W	96 ± 9	None
		288 W	181 ± 13	
Vai et al. 1988	74 ± 10 (4)	50 W	86 ± 14	None
		100 W	96 ± 10	
		150 W	107 ± 22	
		200 W	110 ± 13	

Table A-3. Effect of Exercise Stress on Tidal Volume

Reference	Baseline Value (L) (n)	Stressor Description	Percentage of Baseline	Notes
Artal et al. 1986	0.580 ± 0.250 (39)	34 W	144% (n = 15)	None
		57 W	176% (n = 14)	
		106 W	367% (n = 10)	
Kilbride et al. 2003 women	9.0 ± 2.9 ml/kg (10) (~0.571 L)	40 W	162%	None
		64 W	220%	
		103 W	310%	
		144 W	372%	
		189 ± 11 W	417%	
Takano 1988 30 rpm	0.493 (rest) (12) 0.515 (0 W) (12)	30 W	130%	0 W conditions were described as “unloaded cycling”; 30-75 W outcomes were normalized to “rest” values rather than the 0 W values
		60 W	168%	
		75 W	198%	
Takano 1988		30 W	124%	

Reference	Baseline Value (L) (n)	Stressor Description	Percentage of Baseline	Notes
60 rpm	0.504 (rest) (12) 0.537 (0 W) (12)	60 W	168%	
		75 W	199%	
Walsted et al. 2018	0.882 (rest) (6) 1.014 (0 W) (6)	20 W	120%	0 W conditions were not described; outcomes for non-zero work rates were normalized to the “rest” values rather than the 0 W values
		40 W	137%	
		60 W	153%	
		80 W	176%	
		100 W	194%	
		120 W	201%	
		140 W	225%	
		160 W	239%	
		180 W	255% (4)	
		200 W	276% (4)	
		220 W	282% (4)	
		240 W	269% (4)	
Dorneles et al. 2019	0.701 (10)	20 W	167%	None
		40 W	174%	
		60 W	217%	
		100 W	290%	
		142 ± 35 W	299%	
Chetta et al. 2004	0.61 ± 0.20 (10) (5 min. baseline)	1 min.	148%	Changes during 6 min. walk test
		2 min.	181%	
		3 min.	214%	
		4 min.	231%	
		5 min.	229%	
		6 min.	213%	
Quon et al. 2015	0.91 (19)	20 W	142%	None
		40 W	160%	
		60 W	176%	
		80 W	194%	
		100W	199%	
		192 W	304%	
		235 W	300%	
Quon et al. 2016	0.90 (25)	20 W	145%	Not used for trendline development
		40 W	155%	
		60 W	178%	
		80 W	195%	
		100W	209%	
		196 W	316%	
		237 W	309%	
	0.92 (20)	20 W	120%	None

Reference	Baseline Value (L) (n)	Stressor Description	Percentage of Baseline	Notes
Soumagne et al. 2016		40 W	148%	
		60 W	167%	
		80 W	203%	
		103 W	235%	
		184 W	285%	
Kurtobi et al. 1997	0.59 ± 0.18 (10)	146 ± 9 W	326%	None
Faisal et al. 2015 older	0.73 ± 0.21 (12)	20 W	121%	None
		40 W	154%	
		60 W	183%	
		80 W	206%	
		100 W	252%	
		120 W	279%	
		140 W	305%	
		160 W	332%	
		217 ± 42 W	374%	
Faisal et al. 2015 younger	0.90 ± 0.29 (12)	25 W	140%	None
		50 W	169%	
		75 W	186%	
		100 W	210%	
		125 W	230%	
		150 W	248%	
		175 W	280%	
		238± 48 W	320%	
Amann et al. 2010	1.10 ± 0.22 (5)	50 W	124%	Lower body exercise
		100 W	149%	
		150 W	180%	
		325 W	296%	
	0.90 ± 0.67 (5)	25 W	144%	Upper body exercise
		50 W	178%	
		75 W	222%	
Kilbride et al. 2003 men	10 ± 3.6 L/kg (14) (~0.82 L)	40 W	145%	None
		108 W	180%	
		178 W	210%	
		237 W	262%	
		288 W	297%	
Vai et al. 1988	0.69± 0.07 (4)	50 W	148%	None
		100 W	147%	
		150 W	192%	
		200 W	218%	

Table A-4. Effect of Exercise Stress on Breathing Frequency

Reference	Baseline Value (breaths/min) (n)	Stressor Description	Percentage of Baseline	Notes
Artal et al. 1986	16.1 ± 5.6 (39)	34 W	99% (n = 15)	None
		57 W	176% (n = 14)	
		106 W	239% (n = 10)	
Kilbride et al. 2003 women	16.2 ± 5.1 (10)	40 W	154%	None
		64 W	149%	
		103 W	173%	
		144 W	199%	
		189 ± 11 W	246%	
Takano 1988 30 rpm	16.8 (rest) (12) 22.9 (0 W) (12)	30 W	142%	0 W conditions were described as “unloaded cycling”; 30-75 W outcomes were normalized to “rest” values rather than the 0 W values
		60 W	166%	
		75 W	173%	
Takano 1988 60 rpm	17.1 (rest) (12) 13.2 (0 W) (12)	30 W	148%	
		60 W	175%	
		75 W	186%	
Walsted et al. 2018	13.9 ± 1.2 (rest) (6) 19.8 ± 1.3 (0 W) (6)	20 W	149%	0 W conditions were not described; outcomes for non-zero work rates were normalized to the “rest” values rather than the 0 W values
		40 W	150%	
		60 W	156%	
		80 W	161%	
		100 W	161%	
		120 W	181%	
		140 W	187%	
		160 W	194%	
		180 W	210% (4)	
		200 W	209% (4)	
		220 W	228% (4)	
		240 W	262% (4)	
Dorneles et al. 2019	13.2 ± 2.6 (10)	20 W	102%	None
		40 W	113%	
		60 W	111%	
		100 W	157%	
		142 ± 35 W	212%	
Chetta et al. 2004	19 ± 3 (10) (5 min. baseline)	1 min.	126%	Changes during 6 min. walk test
		2 min.	137%	
		3 min.	125%	
		4 min.	142%	
		5 min.	131%	
		6 min.	152%	
	15 (19)	20 W	133%	None

Reference	Baseline Value (breaths/min) (n)	Stressor Description	Percentage of Baseline	Notes
Quon et al. 2015		40 W	144%	
		60 W	149%	
		80 W	165%	
		100W	180%	
		192 W	220%	
		235 W	306%	
Quon et al. 2016	15 (25)	20 W	130%	Not used for trendline development
		40 W	141%	
		60 W	146%	
		80 W	161%	
		100W	175%	
		196 W	216%	
		237 W	303%	
Soumagne et al. 2016	16 (20)	20 W	111%	None
		40 W	117%	
		60 W	121%	
		80 W	123%	
		103 W	130%	
		184 W	194%	
Kurtobi et al. 1997	17.3 ± 4.4 (10)	146 ± 9 W	191%	None
Faisal et al. 2015 older	16.5 (12)	20 W	146%	None
		40 W	142%	
		60 W	143%	
		80 W	154%	
		100 W	147%	
		120 W	162%	
		140 W	176%	
		160 W	200%	
		217 ± 42 W	286%	
Faisal et al. 2015 younger	16.2 (12)	25 W	118%	None
		50 W	119%	
		75 W	126%	
		100 W	141%	
		125 W	152%	
		150 W	162%	
		175 W	179%	
		238± 48 W	241%	
Amann et al. 2010	10.1 ± 2.0 (5)	50 W	263%	Lower body exercise
		100 W	292%	
		150 W	303%	
		325 W	447%	

Reference	Baseline Value (breaths/min) (n)	Stressor Description	Percentage of Baseline	Notes
	15 ± 2.2 (5)	25 W	167%	Upper body exercise
		50 W	187%	
		75 W	213%	
Kilbride et al. 2003 men	19.2 ± 4.5 (14)	40 W	167%	None
		108 W	187%	
		178 W	213%	
		237 W	167%	
		288 W	187%	
Vai et al. 1988	18.2 ± 2.5 (4)	50 W	103%	None
		100 W	117%	
		150 W	114%	
		200 W	106%	

Table A-5. Effect of Exercise Stress on Inspiratory Duty Fraction

Reference	Baseline Value (dimensionless) (n)	Stressor Description	Percentage of Baseline	Notes
Takano 1988 30 rpm	0.40 (rest) (12) 0.39 (0 W) (12)	30 W	109%	0 W conditions were described as "unloaded cycling"; 30-75 W outcomes were normalized to "rest" values rather than the 0 W values. Calculated by the current analyst as inhalation time/(inhalation time + exhalation time).
		60 W	109%	
		75 W	113%	
Takano 1988 60 rpm	0.40 (rest) (12) 0.41 (0 W) (12)	30 W	103%	
		60 W	113%	
		75 W	114%	
Walsted et al. 2018	0.33 ± 0.03 (rest) (6) 0.42 ± 0.02 (0 W) (6)	20 W	103%	0 W conditions were not described; outcomes for non-zero work rates were normalized to the "rest" values rather than the 0 W values
		40 W	107%	
		60 W	106%	
		80 W	104%	
		100 W	105%	
		120 W	109%	
		140 W	108%	
		160 W	103%	
		180 W	110% (4)	
		200 W	111% (4)	
		220 W	106% (4)	
		240 W	114% (4)	
Chetta et al. 2004	0.38 ± 0.03 (10) (5 min. baseline)	1 min.	116%	Changes during 6 min. walk test
		2 min.	118%	
		3 min.	121%	
		4 min.	121%	

Reference	Baseline Value (dimensionless) (n)	Stressor Description	Percentage of Baseline	Notes
		5 min.	124%	
		6 min.	124%	

Table A-6. Effect of Exercise Stress on Inhalation and Exhalation Time

Reference	Baseline Value (sec) (n)	Stressor Description	Percentage of Baseline
Inhalation time			
Takano 1988 30 rpm	1.51 (rest) (12) 1.05 (0 W)[a] (12)	30 W	76.6%
		60 W	65.7%
		75 W	64.4%
Takano 1988 60 rpm	1.45 (rest) (12) 1.05 (0 W) (12)	30 W	69.8%
		60 W	65.2%
		75 W	60.3%
Exhalation time			
Takano 1988 30 rpm	2.27 (rest) (12) 1.67 (0 W) (12)	30 W	66.3%
		60 W	56.8%
		75 W	52.3%
Takano 1988 60 rpm	2.21 (rest) (12) 1.53 (0 W) (12)	30 W	66.3%
		60 W	53.2%
		75 W	48.1%

[a]0 W conditions were described as “unloaded cycling”; 30-75 W outcomes were normalized to “rest” values rather than the 0 W values.

LIST OF ABBREVIATIONS AND ACRONYMS

BMI	Body mass index
bpm	Beats per minute
CT	Central tendency
NR	Not reported
PBPK	Physiologically based pharmacokinetic
SD	Standard deviation
SEM	Standard error of the mean