Université de Montréal

Taux quotidiens d'inhalation
et paramètres cardio-pulmonaires chez l'humain
selon les données publiées en rapport au double marquage des molécules d'eau
pour l'analyse du risque

par

Pierre Brochu

Département de santé environnementale et santé au travail

Faculté de médecine

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présentée par Pierre Brochu

a été évaluée par un jury composé des personnes suivantes :

Docteur Claude Viau, président-rapporteur

Docteur Kannan Krishnan, directeur de recherche

Docteur Jules Brodeur, codirecteur de recherche

Docteur Marc Baril, membre du jury

Docteur Renaud Vincent, examinateur externe

Docteur Gilbert Blaise, représentant du doyen

Sommaire

L'objectif de cette étude est de déterminer certains paramètres respiratoires et cardiovasculaires chez des sujets de tous âges pour utilisation, à titre d'intrants physiologiques, en modélisation toxicocinétique et en analyse du risque toxique. La base de données utilisée est tirée de la littérature. Il s'agit de mesures portant sur la dépense d'énergie quotidienne de base et la dépense d'énergie quotidienne de totale obtenues, l'une par calorimétrie indirecte, l'autre par double marquage isotopique des molécules d'eau. Selon le type d'unité retenu, les valeurs les plus élevées au 99^e centile des taux quotidiens d'inhalation sont obtenues chez des adolescentes et des femmes âgées de 11 à 55 ans souffrant d'embonpoint ou d'obésité, durant leur 36^e semaine de grossesse (47,31 m^3/jour), ainsi que chez des garçons de poids corporel normal âgés de 2,6 à moins de 6 mois (1,138 m^3/kg-jour) et de 10 à moins de 16,5 ans (22,29 m^3/m^2-jour). Chez les enfants et les adolescents de poids corporel normal âgés de 5 à moins de 16.5 ans, les valeurs pour l'écart entre le 2,5^e au 99^e centile sont généralement plus élevées que celles obtenues chez les sujets plus âgés : taux de ventilation minute, 0,132 à 0,774 L/kg-min ou 4,42 à 21,69 L/m^2-min *versus* 0,076 à 0,461 L/kg-min ou 2,80 à 16,99 L/m^2-min; taux de ventilation alvéolaire, 0,093 à 0,553 L/kg-min ou 3,09 à 15,53 L/m^2-min *versus* 0,047 à 0,312 L/kg-min ou 1,73 à 11,63 L/m^2-min; débit cardiaque, 0,065 à 0,330 L/kg-min ou 2,17 à 9,46 L/m^2-min *versus* 0,045 à 0,201 L/kg-min ou 1,63 à 7,24 L/m^2-min; ratio de ventilation-perfusion, 1,12 à 2,16 *versus* 0,78 à 2,40. Il faut conclure que les apports inhalés en polluants, exprimés en μg/kg-min ou μg/m^2-min sont plus élevés chez les enfants que chez les sujets plus âgés pour des concentrations d'exposition comparables. D'autres données montrent qu'il en est de même pour les apports inhalés par unité de poids corporel chez les femmes enceintes et les femmes qui allaitent par rapport à des sujets males d'âge comparable. L'ensemble des résultats obtenus suggère notamment que les valeurs des $NOAEL_H$ de Santé Canada pourraient être abaissées par un facteur de 2,6 par utilisation du 99^e centile le plus élevé des taux quotidiens d'inhalation chez les enfants; le taux de ventilation minute de 20,83 L/min approximé pour une journée de travail de 8 heures peut être considéré comme étant conservateur ; par contre, l'utilisation du taux quotidien d'inhalation de 0,286 m^3/kg-jour (c.-à-d. 20 m^3/jour pour un adulte de poids corporel de 70 kg) est inappropriée en analyse et gestion du risque lorsqu'appliquée à l'ensemble de la population.

Mots clés : dépense d'énergie, consommation d'oxygène, inhalation, ventilation minute, ventilation alvéolaire, débit cardiaque, ventilation-perfusion, double marquage des molécules d'eau, analyse du risque.

Abstract

The aim of the present study is to determine some respiratory and cardiovascular parameters in subjects of all ages for use, as physiological inputs, in toxicokinetic simulations and toxic risk assessment. The database used is taken from the literature. Data of interest include basal energy expenditures and total daily energy expenditures obtained by indirect calorimetry and doubly labeled water measurements respectively. Depending upon the unit value chosen, the highest 99th percentiles for daily inhalation rates were found in overweight/obese females 11 to 55 years old during their 36th weeks of pregnancy (47.31 m^3/day), as well as in normal-weight boys aged 2.6 to less than 6 months (1.138 m^3/kg-day) and 10 to less than 16.5 years (22.29 m^3/m^2-day). Generally higher values for the 2.5th up to 99th percentile were found in normal-weight children and teenagers aged 5 to less than 16.5 years compared to those for older individuals: minute ventilation rate, 0.132 to 0.774 L/kg-min or 4.42 to 21.69 L/m^2-min *versus* 0.076 to 0.461 L/kg-min or 2.80 to 16.99 L/m^2-min; alveolar ventilation rate, 0.093 to 0.553 L/kg-min or 3.09 to 15.53 L/m^2-min *versus* 0.047 to 0.312 L/kg-min or 1.73 to 11.63 L/m^2-min; cardiac output, 0.065 to 0.330 L/kg-min or 2.17 to 9.46 L/m^2-min *versus* 0.045 to 0.201 L/kg-min or 1.63 to 7.24 L/m^2-min; ventilation-perfusion ratio, 1.12 to 2.16 *versus* 0.78 to 2.40. Higher intakes of air pollutants by the respiratory tract expressed in μg/kg-min or μg/m^2-min are expected in children compared to older individuals for identical exposure concentrations. The same conclusion is reached in pregnant and lactating females compared to male subjects of same ages, for intakes expressed per unit of bodyweight. The aggregate results obtained notably suggests that $NOAEL_H$ values from Health Canada could be decreased by a factor of 2.6 by the use of the highest

99th percentiles for daily inhalation rates found in children; the minute ventilation rate of 20.83 L/min approximated based on an 8-hour workday may be considered as being conservative; however, the use of the daily inhalation rate of 0.286 m^3/kg-day (i.e. 20 m^3/day for a 70-kg adult) is inappropriate in risk assessment and management when applied to the whole population.

Keywords: energy expenditure, oxygen consumption, inhalation, minute ventilation, alveolar ventilation, cardiac output, ventilation-perfusion, doubly labeled water, risk assessment.

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LISTE DES SIGLES ET DES ABRÉVIATIONS

A	Ratio AEA/TMB (paramètre A)
AEA	Apport énergétique alimentaire
α	Données pour l'ensemble des activités de la journée des individus
β	Données pour des individus au repos
BTPS	Température corporelle, pression barométrique au niveau de la mer et saturation en vapeurs d'eau
CaO_2	Contenu artériel en oxygène
CO_2	Bioxyde de carbone
CvO_2	Contenu veineux en oxygène
DEQT	Dépense énergétique quotidienne totale
^2H	Deutérium (ou D)
DAVO	Différence artérioveineuse en oxygène
DMIME	Double marquage isotopique des molécules d'eau
E	Dépense d'énergie
F	Ratio du taux de la dépense énergétique durant des périodes actives sur la valeur estimée du TMB
fc	Fréquence cardiaque
fr	Fréquence respiratoire
H	Volume d'oxygène consommé à STPD (L) pour produire une dépense d'énergie de 1 kcal: H_J la nuit (sujets à jeun), H_P le jour (phase postprandiale)
HCO_3^-	Ion bicarbonate
H_2CO_3	Acide carbonique
i	Niveau d'activité durant la journée
k	Nombre de niveaux d'activité durant la journée

MET	Équivalent métabolique (multiplicateur du TMB)
N	Taux d'excrétion d'azote urinaire
^{18}O	Oxygène lourd-18
PCBP	Pharmacocinétique à base physiologique
PiO_2	Proportion d'oxygène inspirée
PeO_2	Proportion d'oxygène expirée
Q	Débit cardiaque
RER	Ratio d'échange respiratoire VCO_2/VO_2
Sld	Période de sommeil durant la nuit
STPD	Température standard, pression barométrique au niveau de la mer pour des gaz sec
TAV	Approche basée sur la compilation des VE sur 24 heures
T_i	Période moyenne de temps allouée à chaque niveau i d'activité
TMB	Taux métabolique de base
TQI	Taux quotidien d'inhalation
VA	Taux de ventilation alvéolaire à BTPS
VDphys	Espace mort physiologique
VE	Taux de ventilation minute à BTPS
VE_i	VE moyen pour chaque niveau i d'activité
VCO_2	Taux de production de bioxyde de carbone à STPD
VO_2	Taux de consommation d'oxygène à STPD
VP	Volume propulsé après chaque battement cardiaque
VQ	Équivalent ventilatoire, ratio de VE (L/min.) à BTPS sur le VO_2 (L/min.), donc VE/VO_2 (sans unité)
VT	Volume courant

DEDICACE

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CHAPITRE PREMIER :

1 INTRODUCTION GENERALE

1.1 EFFETS DES POLLUANTS DE L'AIR SUR LA POPULATION

Les xénobiotiques environnementaux de l'air extérieur qui sont inhalés génèrent des manifestations toxiques chez des individus de tous âges (Schwartz *et al.* 1991; Sunyer *et al.* 1991; Abbey *et al.* 1993; Neher et Koenig 1994; Braun-Fahrländer *et al.* 1997; Sheppard *et al.* 1999; Tolbert *et al.* 2000; Liu *et al.* 2003; Yang *et al.* 2003). Ils contribuent également à augmenter les taux de mortalité de la population (Burnett *et al.* 1998; Loomis *et al.* 1999; Samet *et al.* 2000). Chez les femmes enceintes, les polluants de l'air inhalés et absorbés peuvent être transférés à l'embryon ou au fœtus via le cordon ombilical. Plus tard, ils peuvent être véhiculés au nouveau-né par l'allaitement (Scialli 1992). Il peut en résulter des nouveau-nés prématurés, de faibles poids corporels (Bobak 2000; Maisonet *et al.* 2001) ainsi que des cas de mortalité post-néonatale (Woodruff *et al.* 1997). Enfin, les travailleurs sont susceptibles d'être exposés à de plus fortes concentrations d'agents toxiques que ne l'est la population en général (Lauwerys 1990). Ainsi donc, tous les individus, de la naissance à l'âge adulte, sont exposés à des contaminants toxiques de l'environnement. Dans le but de déterminer avec précision la charge corporelle de ces contaminants et éventuellement caractériser le risque toxicologique, il importe d'abord de connaître la valeur des paramètres physiologiques critiques tels le taux quotidien d'inhalation, le taux de ventilation minute, le taux de ventilation alvéolaire et le débit cardiaque.

1.2 PARAMETRES UTILISES EN ANALYSE ET EN GESTION DU RISQUE

Les taux quotidiens d'inhalation (TQI), les taux de ventilation minute (VE) et les taux de ventilation alvéolaire (VA) sont largement utilisés pour calculer les niveaux de concentration sans effet néfaste observable ($NOAEL_H$) et les plus faibles niveaux de concentration avec effet néfaste observable ($LOAEL_H$) chez l'humain, pour les composés toxiques de l'air extérieur et intérieur. Ces $NOAEL_H$ et $LOAEL_H$ (en µg/m^3) sont calculés en utilisant les mesures d'exposition des animaux de laboratoire à ces xénobiotiques ($NOAEL_A$ et $LOAEL_A$ respectivement). À cet égard, Santé Canada utilise un TQI exprimé en unité de poids corporel (en m^3/kg-jour), tandis que l'Agence de Protection Environnementale (EPA) des États-unis (USEPA 1994) utilise des VE et des VA exprimés en unité de surface des voies respiratoires (en L/min-cm^2). Par ailleurs, ces surfaces sont fréquemment estimées par l'EPA selon les poids corporels des individus.

Santé Canada calcule des $NOAEL_H$ à partir des $NOAEL_A$ (en µg/m^3) en utilisant un TQI de 0,444 m^3/kg-jour pour des enfants âgés de 5 à 11 ans (12 m^3/jour pour un poids corporel de 27 kg) via la relation suivante (Health Canada 1996):

$$NOAEL_H = NOAEL_A \left(\frac{TQI_A}{P_A} \right) \left(\frac{P_H}{TQI_H} \right) \times a / 24 \times b / 7 \qquad \text{Équation 1}$$

où,

TQI = taux quotidien d'inhalation (m^3/jour);

P = poids corporel (kg);

a = nombre d'heure d'exposition de l'animal au xénobiotique par jour (heure);

b = nombre de jour d'exposition de l'animal au xénobiotique par semaine (jour);

A, H = indices pour identifier les données de l'animal et de l'homme respectivement.

L'EPA calcule des concentrations équivalentes chez l'humain ($NOAEL_{[HEC]}$ synonyme de $NOAEL_H$ en µg/m^3) à partir des $NOAEL_A$ en utilisant des facteurs d'ajustement dosimétrique (FAD) dans l'équation suivante (USEPA 1994):

$$NOAEL_{[HEC]} = NOAEL_A \times a/24 \times b/7 \times (FAD)$$ Équation 2

Les valeurs des FAD (sans unité) varient selon les propriétés des composés toxiques et la région des voies respiratoires affectée par ces derniers. En ce sens, plusieurs équations ont été développées. Par exemple, les FAD pour les composés toxiques qui ne s'accumulent pas significativement dans le sang et qui ont des effets au niveau des voies respiratoires supérieures (extra-thoraciques ou ET), inférieures (trachéo-bronchiques ou TH) ou pulmonaires (PU) se calculent en utilisant les équations 3, 4 et 5 respectivement :

$$FAD_{ET} = \frac{(Dose_{ET})_A}{(Dose_{ET})_H} = \frac{\left(VE/SA_{ET}\right)_A \left(1 - e^{\frac{-Kg_{ET} \times SA_{ET}}{VE}}\right)_A}{\left(VE/SA_{Et}\right)_H \left(1 - e^{\frac{-Kg_{ET} \times SA_{ET}}{VE}}\right)_H}$$ Équation 3

$$FAD_{TB} = \frac{(Dose_{TB})_A}{(Dose_{TB})_H} = \frac{\left(VE/SA_{TB}\right)_A}{\left(VE/SA_{TB}\right)_H} \frac{(fp_{ET})_A}{(fp_{ET})_H} \frac{\left(1 - e^{\frac{-Kg_{TB} \times SA_{TB}}{VE}}\right)_A}{\left(1 - e^{\frac{-Kg_{TB} \times SA_{TB}}{VE}}\right)_H}$$ Équation 4

$$FAD_{PU} = \frac{(Dose_{PU})_A}{(Dose_{PU})_H} = \frac{\left(\frac{Kg_{PU} \times SA_{PU}}{Kg_{PU} \times SA_{PU} + VA}\right)_A \left(\frac{VA}{SA_{PU}}\right)_A}{\left(\frac{Kg_{PU} \times SA_{PU}}{Kg_{PU} \times SA_{PU} + VA}\right)_H \left(\frac{VA}{SA_{PU}}\right)_H} \frac{(fp_{TB})_A}{(fp_{TB})_H} \frac{(fp_{ET})_A}{(fp_{ET})_H}$$ Équation 5

où,

VE, VA = taux de ventilation minute et alvéolaire respectivement (L/min);

SA = surface des voies respiratoires concernées (cm^2);

Kg = cœfficient de transport (cm/min);

fp = fraction du xénobiotique pénétrant dans les voies respiratoires concernées.

Le VE retenu par l'EPA chez l'humain est de 13,88 L/min (USEPA 1994). Cette valeur a été estimée en divisant le TQI de 20 m^3/jour pour un adulte par 1440 minutes. Le VA retenu par l'EPA de 9,7 L/min chez l'humain a été estimé en multipliant le VE estimé de 13,88 L/min par 70% (USEPA 1994). Les mêmes équations 1 et 2 sont utilisées pour calculer les $LOAEL_H$ et $LOAEL_{[HEC]}$ (synonyme de $LOAEL_H$) à partir des résultats d'exposition chez l'animal ($LOAEL_A$ en µg/m^3). Lorsque disponibles, les $NOAEL_H$ et $LOAEL_H$ mesurés chez l'humain sont préférés à ceux estimés à partir des données chez l'animal. La division des $NOAEL_H$, $NOAEL_{[HEC]}$, $LOAEL_H$ et $LOAEL_{[HEC]}$ par un ou plusieurs facteurs de sécurité permet de calculer des critères, des normes et des concentrations de référence (RfC) pour la qualité de l'air. Ces derniers fixent des limites pour les concentrations des composés toxiques dans l'air ambiant (en µg/m^3), ces dernières ne devant pas dépasser un seuil « considéré comme étant sécuritaire» pour la population. L'un ou plusieurs des facteurs de sécurité suivants peut ou peuvent être utilisé(s) selon le niveau de précision du LOAEL ou NOAEL retenu (McColl *et al.* 1989 ; Dourson *et al*. 2002 ; WHO 2005) :

F_1 = facteur de variabilité intra-espèce pour tenir compte des différences de sensibilité chez l'humain exposé aux mêmes xénobiotiques selon les mêmes conditions d'exposition (valeur courante de 10 subdivisée en deux facteurs de $10^{0,5}$ (3,16) pour les différences toxicodynamiques et toxicocinétiques, respectivement) ;

F_2 = facteur de variabilité inter-espèce lors de l'utilisation d'un $NOAEL_A$, pour tenir compte des différences en sensibilité chez l'animal par rapport à l'humain pour les mêmes xénobiotiques (valeur courante de 10 subdivisée en deux facteurs, l'un de $10^{0,4}$ (2,5) pour les différences toxicodynamiques, l'autre de $10^{0,6}$ (4,0) pour celles toxicocinétiques) ;

F_3 = facteur d'ajustement pour étude sub-chronique (par exemple, période de 90 jours chez le rat au lieu de période de 180 à 360 jours) pour tenir compte de la possibilité que des effets puissent survenir à des doses inférieures lors d'une exposition plus longue (valeur courante de 10) ;

F_4 = facteur pour utilisation d'un LOAEL au lieu d'un NOAEL ou pour extrapoler un NOAEL à partir d'un LOAEL (valeur courante de 10) ;

F_5 = facteur retenu lorsque les données expérimentales chez l'animal sont scientifiquement valables, mais incomplètes pour aborder adéquatement toutes les possibilités d'effets néfastes d'intérêt (valeur courante de 10);

F_6 = facteur modifiant permettant de tenir compte de la qualité de la base des données utilisées (incertitude non considérée dans le facteur F_5; par exemple, le nombre d'animaux testé) et du jugement professionnel de l'évaluateur sur l'ensemble du processus de calcul d'un critère, d'une norme ou d'une RfC (1 à 10 avec valeur par défaut de 1).

Les moyennes et/ou les centiles des TQI (en m^3/jour ou m^3/kg-jour) sont également utilisés pour calculer les degrés d'exposition (apports inhalés) des individus de différentes strates d'âge de la population aux xénobiotiques (C_{Exp} en $\mu g/m^3$) contenus dans l'air extérieur et/ou l'air intérieur (De Brouwere *et al*. 2007; van Engelen et Prud'homme de Lodder 2007; Schleier *et al.* 2008), comme c'est le cas dans des études épidémiologiques sur la prévalence des maladies respiratoires et cardiovasculaires chez l'humain (Pope *et al.* 2009). Ces degrés d'exposition (D_{Exp} en µg/jour ou en µg/kg-jour) sont calculés en multipliant les concentrations de xénobiotiques dans l'air (C_{Exp} en µg/m^3) par les valeurs des TQI (en m^3/jour ou m^3/kg-jour), tel qu'exprimé par l'équation suivante :

$$D_{Exp} = C_{EXp} \times TQI \qquad \text{Équation 6}$$

Les D_{Exp} (en µg/jour ou en µg/kg-jour) des individus durant de courtes périodes d'exposition aux concentrations de xénobiotiques (en µg/L) de l'air extérieur et/ou en milieu de travail sont calculés en remplaçant les TQI de l'équation 6 par des VE (en L/min ou L/kg-min). Les VE utilisés ont été mesurés chez des sujets au repos et lors d'exercice afin de caractériser les différents niveaux d'intensité d'activités durant la journée; d'autres ont été approximés pour décrire l'ensemble des activités de la journée en divisant un TQI par 1440 minutes. Un VE de 20,83 L/min a été estimé pour calculer les D_{Exp} des travailleurs aux xénobiotiques de l'air en milieu de travail (Paustenbach 2001). Les VE sont également utilisés dans le processus de calcul et éventuellement de révision de normes en milieu de travail (Clayton et Clayton 1982; Lauwerys 1990). Enfin, les VA (en L/min) et les débits cardiaques (Q en L/min) sont essentiels à la modélisation pharmacocinétique à base physiologique (PCBP) afin de comprendre et de prédire les comportements des composés toxiques exogènes dans le corps et de calculer leurs doses internes et celles de leurs métabolites (Krishnan et Andersen 2001). Les paramètres VE, VA, Q et le ratio VA/Q sont identifiés, pour les besoins de la présente thèse, comme étant des « paramètres cardio-pulmonaires ».

1.3 TAUX QUOTIDIENS D'INHALATION

Le TQI, exprimé en m^3/jour, est le produit de la valeur de VE (l/min) pour l'ensemble des activités sur 24 heures par une période de 1440 minutes. Dans les faits cependant, les VE se mesurent à l'aide d'un spiromètre chez des sujets qui effectuent des activités pendant de courtes périodes de temps, car l'appareil est trop encombrant et inconfortable pour être porté par des individus pendant des périodes de 24 heures (Durnin et Passmore 1967; Garcia *et al.* 2009a). Deux approches ont donc été élaborées pour estimer des TQI en fonction de l'âge des individus. La première approche nécessite la compilation des VE et de la durée des périodes de différentes activités pendant 24 heures, la seconde est basée sur la conversion des dépenses d'énergie quotidienne en TQI. Ces approches et les biais qu'elles génèrent dans le processus de calculs des TQI sont présentés et analysés en détail dans Brochu *et al.* (2006c). Cette analyse s'appuie sur une revue exhaustive des données publiées et elle comprend, dans le cas des deux approches, un calcul des niveaux d'erreurs des centiles et/ou des moyennes des TQI de la littérature (n=253). Ces mesures découlent de données obtenues, à l'aide de la méthode du double marquage isotopique des molécules d'eau, chez 1252 sujets de poids corporel normal âgés de 2,6 mois à 96 ans et qui vaquent librement à leur occupation pendant plus de 20 000 journées.

1.3.1 Approche basée sur la compilation des VE

Les valeurs de VE retrouvées dans la littérature pour différents niveaux d'exigence physique représentatifs des activités effectuées sur une période de 24 heures (sommeil, niveaux d'activité très légère, légère, modérée et exigeante), chaque activité étant d'une durée donnée, permet de calculer des TQI selon la relation mathématique suivante (Brochu *et al.* 2006c):

$$TQI = \left[\sum_{i=1}^{k} VE_i \times T_i \right] \times 10^{-3}$$ Équation 7

où,

TQI = taux quotidien d'inhalation (m^3/jour);

VE_i = taux moyen de ventilation minute pour chaque niveau *i* d'activité (L/min.);

T_i = période moyenne de temps allouée à chaque niveau *i* d'activité (min./jour);

i = identification du niveau d'activité durant la journée;

k = nombre de niveaux d'activité durant la journée;

10^{-3} = facteur de conversion des litres en m^3.

Cette approche communément représentée par TAV pour « temps activité ventilation » a été utilisée pour calculer des valeurs centrales des TQI sans mention de valeur moyenne, ni d'écart-type (Roy et Courtay 1991) et pour déterminer des distributions de centiles des TQI (Allan 1995; Richardson 1997; Allan et Richardson 1998; Allan *et al.* 2008).

1.3.1.1 *Biais et imprécisions en rapport aux valeurs de VE et T*

La détermination des valeurs appropriées pour VE et T, pour chaque niveau d'activité et chaque groupe d'âge, est un défi de taille. On retrouve dans la littérature plus de mesures de VE pour des sujets au repos que pour des sujets actifs. Peu de valeurs de VE et de T ont été mesurées chez les enfants, les adolescents, les sujets du sexe féminin; de plus, les données statistiques habituelles (moyenne, écart-type avec le nombre de sujets) sont rarement disponibles (Allan 1995; Brochu *et al.* 2006c). Cette absence de données pertinentes impose que l'on se prête à divers calculs d'interpolation et d'extrapolation de données approximatives et conservatrices que l'on qualifie souvent de « non orthodoxes »

(Allan 1995). Il en résulte, en bout de ligne, des biais sur certains VE et T calculés et, conséquemment, sur les valeurs des TQI estimées (Allan 1995; Allan et Richardson 1998). À titre d'exemple, les VE pour la période de sommeil et de repos (niveau 1 d'exigence physique) estimés par Allan et Richardson (1998) chez des individus âgés de 7 mois à plus de 60 ans correspondent à des équivalents métaboliques (MET) variant de 1,2 à 1,6, alors que des valeurs de l'ordre de 1 auraient dû être utilisées (Brochu *et al.* 2006c). Ce biais de surestimation qui a d'ailleurs été incorporé dans les calculs de Allen *et al.* (2008) a eu un impact important sur l'ordre de grandeur des valeurs des TQI que ces auteurs ont estimées, car la somme des périodes de sommeil et de repos (niveau 1) pour chaque groupe d'âge représente plus de 60% d'une journée de 24 heures.

L'imprécision associée aux mesures expérimentales des VE par spirométrie contribue également à biaiser les TQI estimés selon l'approche TAV. Par exemple, la plupart des sujets soumis à la spirométrie augmentent inconsciemment leur volume courant afin de maintenir une ventilation adéquate après l'installation de l'embouchure, de la pince à nez ou encore du masque facial (Brochu *et al.* 2006c). Certains d'entre eux augmentent également leurs fréquences respiratoires. D'autres facteurs tels le stress, la température ambiante et la fièvre influencent aussi la précision des mesures des VE (Brochu *et al.* 2006c). Certaines précautions doivent donc être prises afin de mesurer adéquatement les VE pour chaque groupe d'âge, particulièrement chez les enfants au repos (Brochu *et al.* 2006c).

1.3.1.2 *Lacunes au niveau des connaissances*

L'approche TAV intègre dans ses calculs uniquement les VE pour des activités pouvant être reproduites en clinique (par ex. le sommeil, la marche et la course). Elle ne tient pas compte des gestes involontaires. De tels gestes nécessitent chez un adulte une dépense d'énergie de 350 kcal/jour et sont responsables d'une sous-estimation de 2,0 m^3/jour sur un TQI estimé (Brochu *et al*. 2006c). L'approche TAV ne tient pas nécessairement compte des besoins en oxygène nécessaires à la thermogenèse et au processus de la croissance des individus de la naissance jusqu'à l'état d'adulte (Brochu *et al*. 2006c). En bout de piste, le mélange aléatoire de données sous-estimées et de plusieurs données surestimées se traduit par des moyennes et des centiles de TQI sous- ou surestimés de -47 à +121%, respectivement, (Brochu *et al*. 2006c) pour Richardson (1997) et pour Allan et Richardson (1998). Le plus récent article de ces auteurs dans lequel ils utilisent l'approche TAV (Allen *et al.* 2008) conclut encore à des TQI moyens qui sont physiologiquement irréalistes. Par exemple, le TQI des enfants âgés de moins de 7 mois est sous-estimé par un facteur de 1,6 et même trop faible pour maintenir ces derniers en vie lors de repos (Brochu *et al.* 2006c), alors que ceux des enfants âgés de 7 mois à 4 ans et de 5 à 11 ans sont surestimés par un facteur de 1,8 et 1,6 respectivement.

1.3.2 Approche basée sur la conversion des dépenses d'énergie

Les valeurs de VE mesurées durant les protocoles expérimentaux (Layton 1993) correspondent aux volumes d'air exhalé par minute. Ces volumes d'air ont été préalablement inhalés, réchauffés à la température corporelle et humidifiés dans les voies respiratoires (saturation en vapeur d'eau). Les volumes par minute des VE sont donc exprimés sous des conditions standards de température corporelle, de pression barométrique au niveau de la mer et de saturation en vapeurs d'eau (BTPS). Les VE varient en fonction des fréquences respiratoires et du volume courant selon la relation suivante (Layton 1993) :

$$VE = fr \times VT \qquad \text{Équation 8}$$

VE = taux de ventilation minute à BTPS (L/min);

fr = fréquence respiratoire (nombre de respirations/minute);

VT = volume courant (L).

Les taux de consommation d'oxygène (VO_2) sont exprimés sous des conditions standards de température, de pression barométrique au niveau de la mer et pour des gaz secs (STPD) en fonction des VE selon la relation suivante (Seear *et al.* 1994):

$$VO_2 = VE(PiO_2 - PeO_2) \qquad \text{Équation 9}$$

Où,

VO_2 = taux de consommation d'oxygène à STPD (L of O_2/min);

PiO_2 = proportion d'oxygène dans l'air inspirée (sans unité);

PeO_2 = proportion d'oxygène dans l'air expirée (sans unité).

Layton (1993) décrit dans une seule équation l'ensemble de ces concepts physiologiques en faisant intervenir les paramètres pertinents soit la dépense d'énergie et le volume d'air inhalé chez les individus aussi bien lors de courtes (VE) que de longues périodes de temps (TQI). Cette équation, tout à fait innovatrice, deviendra la procédure privilégiée pour déterminer les TQI au détriment de l'approche TAV (Finley *et al.* 1994; NCEA 2006; Arcus-Arth et Blaisdell 2007; Stifelman 2007; USEPA 2008) :

$$TQI = E \times H \times VQ \times 10^{-3} \qquad \text{Équation 10}$$

où,

E = dépense d'énergie (kcal/jour);

H = volume d'oxygène consommé à STPD (L) pour produire une dépense d'énergie de 1 kcal ;

VQ = équivalent ventilatoire, ratio de VE (L/min.) à BTPS sur le VO_2 (L/min.), donc VE/VO_2 (sans unité).

1.3.2.1 *Biais et imprécisions en rapport avec les valeurs de E*

Les trois approches qui ont été développées par Layton (1993) pour estimer les valeurs des E sont biaisées et ces biais génèrent des erreurs sur les TQI variant de -36 à +60% (Brochu *et al*. 2006c). La première approche permet d'estimer les valeurs de E en compilant les MET et les taux métaboliques de bases (TMB, en kcal/min) par niveaux d'exigence physique pendant leurs durées respectives :

$$E = [\sum_{i=1}^{k} MET_i \times T_i \times TMB_i] \qquad \text{Équation 11}$$

Cette approche est entachée des mêmes difficultés relatives à l'obtention de données pertinentes, comme c'est le cas pour l'approche TAV : elle exclut les coûts énergétiques de la thermogenèse, de la croissance et ceux occasionnés par les gestes involontaires (Brochu *et al.* 2006c). Les valeurs des TMB qui sont estimées pour les divers groupes d'âge, en incorporant les poids corporels des individus dans les équations de Schofield (1985), sont également biaisées par -19 à +13% (Brochu *et al.* 2006c).

Dans une deuxième approche, Layton (1993) utilise les apports énergétiques alimentaires (AEA) compilés lors d'enquêtes sur les diètes alimentaires des Américains afin de décrire les valeurs de E pour différents groupes d'âges. Il assume que les valeurs des AEA des diètes alimentaires sont égales aux valeurs des E sur une base quotidienne. Cette approche minimise le nombre de biais et optimise la précision des valeurs obtenues pour E. Par contre, elle ne tient pas compte des pertes alimentaires dans les fèces, les gaz intestinaux et l'urine, lesquelles peuvent atteindre -12,2% (Brochu *et al.* 2006c), ni du fait que les individus ingèrent quotidiennement plus de nourriture que ce qui est requis pour leurs besoins énergétiques. C'est entre autre le cas pour 65% des adultes Américains qui souffrent de surplus de poids (NCHS 2003). De plus, il est reconnu que des données rapportées dans les enquêtes nutritionnelles sont biaisées par -45 à +21% (Brochu *et al.* 2006c).

Comme troisième approche, Layton (1993) utilise l'ordre de grandeur des ratios AEA/TMB (A ou Paramètre A) des sujets pour calculer les valeurs de E via les équations suivantes :

$$A = [(24 - Sld)F + Sld]/24 \qquad \text{Équation 12}$$

$$F = (24A - Sld)/(24 - Sld) \qquad \text{Équation 13}$$

$$E = A \times TMB \qquad \text{Équation 14}$$

où,

F = ratio du taux de la dépense énergétique durant des périodes actives sur la valeur estimée du TMB (sans unité);

Sld = temps alloué pour le sommeil durant la nuit (heure/jour).

On retrouve dans cette approche les mêmes biais relatifs à l'estimation des AEA et des TMB dans les calculs des valeurs des E que ceux identifiés pour l'une ou l'autre des deux premières approches (Brochu *et al.* 2006c).

1.3.2.2 *Lacunes au niveau des connaissances en rapport avec la valeur de H*

En calculant les différentes proportions de protéines, de lipides et de carbohydrates qui sont ingérées à partir de l'alimentation des américains, Layton (1993) a déterminé qu'un volume de 0,21 L d'oxygène (O_2) était consommé pour chaque kcal d'énergie dépensée, et ce pour l'ensemble de la population (n=51 092). Cette valeur de H a été calculée en considérant que l'oxydation de 1 gramme de protéines, de lipides et de carbohydrates ingérés nécessitait la consommation de 0,97, 0,83 et 2,0 L d'oxygène pour générer 4,5, 9,5 et 4,2 kcal respectivement (Brochu *et al.* 2006c). Layton a donc considéré que la combustion de carbohydrates, de protéines et de lipides de la diète alimentaire nécessitait, respectivement, 0,199, 0,212 et 0,221 L de O_2 consommé par kcal d'énergie dépensée. Par ailleurs, Layton ne tient pas compte des taux d'absorption des nutriments dans le tractus gastro-intestinal dans ses calculs. Il assume que ce qui est ingéré est complètement absorbé. Il utilise également la valeur de 0,21L de O_2/kcal comme étant une constante physiologique universelle sans au préalable avoir vérifié les possibilités de variation des valeurs de H en fonction de l'âge et du sexe des sujets, ni en fonction des différentes diètes selon les habitudes alimentaires d'un pays à un autre à travers le monde. De plus, en utilisant une valeur de H calculée durant la phase postprandiale pour extrapoler des taux d'inhalation sur une base de 24 heures, Layton assume que la valeur de H est indépendante de l'état de jeûne. Par ailleurs, l'ordre de grandeur de H lors de jeûne varie selon les combustibles métaboliques qui sont mobilisés et oxydés. Chez des sujets à jeun, la combustion de glycogène, de glucose, d'acide hydroxy-3 butyrique, d'acide acétoacétique et triacylglycérol requiert 0,198, 0,200, 0,210, 0,211 et 0,214 L d'O_2/kcal respectivement (Elia 1997).

1.3.2.3 *Lacunes au niveau des connaissances et biais en rapport avec la valeur de VQ*

Layton a opté pour le calcul d'une valeur globale pour l'ensemble des adultes de tous âges en divisant les valeurs des VE par celles des VO_2 (donc VE/VO_2, sans unité) à partir de valeurs mesurées simultanément chez des mêmes adultes, et ce pour un large éventail de VO_2 variant entre 0,24 et 6 L/min. Il en résulte un VQ de 27 (sans unité) que Layton utilise comme constante physiologique pour calculer les TQI des individus âgés de moins de 1 an jusqu'à plus de 75 ans. L'utilisation de cette valeur pour l'estimation des TQI est devenue une pratique courante pendant près de quinze ans (Layton 1993; Finley *et al.* 1994; Brochu *et al.* 2006c; NCEA 2006; Stifelman 2007). Dans les faits, cette valeur ne tient pas compte des caractéristiques physiologiques (VE et VO_2) des enfants et des adolescents; elle ne permet même pas de décrire adéquatement une population normale d'adultes, la moitié des données de la cohorte de Layton (1993) ayant été mesurée chez des athlètes. De plus, la valeur de VQ a été calculée pour un nombre très limité de sujets totalisant seulement 75 adultes. Tel qu'il sera démontré au chapitre quatrième, l'ensemble des activités des individus âgés de 2,6 mois à 96 ans nécessite sur la base d'une période de 24 heures, des valeurs de VO_2 qui sont inférieures à 1 L/min. Les mesures de VE et VO_2 pour des VO_2 variant entre 1 et 6 L/min ont donc biaisé l'estimation du VQ de Layton (1993).

1.3.2.4 *Lacunes au niveau statistique*

Les valeurs de E, VQ, H et de TQI qui ont été calculées par Layton (1993) correspondent à des valeurs moyennes, communément considérées comme des valeurs centrales, sans écart-type, sans précision sur les valeurs minimales et maximales. Cette lacune statistique bien entendu affecte la précision des centiles minimaux et maximaux des TQI calculés par Finley *et al.* (1994) et le NCEA (2006) lors de simulations de Monte Carlo basées sur les approches de Layton (1993).

1.3.3 Biais d'estimation des TQI par unité de poids corporel

Des biais sont générés en divisant le TQI (en m3/jour) d'une cohorte d'individus par le poids corporel d'une autre cohorte de sujets du même âge, afin d'estimer les TQI par unité de poids corporel (en m^3/kg-jour) pour les différents groupes d'âge, et ceci, dans le processus de calcul des deux approches connues (voir sections 1.3.1 et 1.3.2).

1.3.4 Lacunes au niveau des connaissances sur les TQI pour les sujets « à risque »

Les moyennes et les centiles des TQI des individus physiologiquement susceptibles d'inhaler plus d'air, donc plus de polluants de l'air, par jour (par exemple : obèses et athlètes) et par unité de poids corporel (par exemple sujets anorexiques, nouveau-nés, femmes enceintes et en lactation) n'ont jamais été publiés dans la littérature. Cette lacune explique notamment l'absence de modalité règlementaire visant à assurer 1) que les apports inhalés en polluants de l'air et les doses internes qui en résultent (enrichies par la mobilisation des stocks des tissus adipeux et osseux) n'excèdent pas les seuils sécuritaires pour les femmes enceintes et en lactation et 2) que les doses internes disponibles de xénobiotiques ne portent pas atteinte au développement et à la santé aussi bien du fœtus que du nouveau-né allaité.

1.3.5 Impact des biais et des lacunes au niveau des connaissances sur les TQI

L'utilisation des TQI de la littérature biaise notamment les valeurs des $NOAEL_H$ et $NOAEL_{[HEC]}$ estimés à partir des mesures effectuées chez l'animal, biaise également les évaluations des apports inhalés et absorbés en polluants de l'air par la population et affecte ainsi la justesse des décisions à prendre en matière de gestion du risque, d'autant plus que les sujets vraiment à risque d'inhaler plus de polluants de l'air sont exclus. Il en résulte un biais en rapport avec l'établissement de critères, de normes et de concentrations de référence (RfC) de qualité de l'air dont les valeurs sous-estiment le risque à la santé pour certains sujets de la population (Brochu *et al.* 2006c).

Les valeurs disparates de TQI publiés contribuent à l'absence de consensus parmi les organismes œuvrant en environnement et en santé publique (par exemple Santé Canada et EPA) quand à l'indentification du sujet type à protéger, de façon prioritaire, contre les effets d'une concentration donnée de polluants atmosphériques en tant que valeur conservatrice pour l'ensemble de la population. Par exemple, Santé Canada (Health Canada 1996) a retenu pour sa part les garçons âgés de 5 à 11 ans (TQI de 12 m^3/jour pour un poids de 27 kg selon Allan 1995), tandis l'USEPA (2000) a retenu les enfants de moins de 1 an (4,5 m^3/jour pour un poids de 7,6 kg selon Layton 1993). Inévitablement, de telles disparités sur les valeurs des TQI retenues peuvent aboutir à des critères et des normes de qualité de l'air différents pour des xénobiotiques identiques, même si les données toxicologiques considérées lors des calculs sont les mêmes.

1.4 PARAMETRES CARDIO-PULMONAIRES

Les VE, les Q et quelques rares VA ont été mesurés chez des sujets effectuant divers exercices (voir chapitre cinquième). Par contre, aucune étude n'a déterminé les moyennes et les centiles des VE, des Q et des VA pour l'ensemble des activités de la journée des sujets. Les VA et les Q n'ont jamais, non plus, été déterminés sur une base de 24 heures.

Les VE (L/min) nécessaires pour évaluer les apports inhalés en polluants environnementaux durant l'ensemble des activités de la journée des individus sont estimés en divisant les TQI par 1440 minutes (Thompson *et al*. 2008; Garcia *et al.* 2009a). Ces VE sous-estiment les apports inhalés durant la journée compte tenu que les valeurs des TQI incluent les VE relativement faibles durant la nuit avec ceux qui sont plus élevés durant le jour (Brochu *et al.* 2006c; Garcia *et al.* 2009a). Le VE de 20,83 L/min couramment utilisé en évaluation et gestion du risque toxicologique chez l'adulte en milieu de travail a été estimé en assumant que des adultes inhalaient 10 m^3 pendant une période de travail de 8 heures (Paustenbach 2001). La détermination des centiles des VE pour l'ensemble des activités de la journée des adultes permettrait donc de valider, aussi les VE utilisés en gestion et évaluation du risque toxicologique pour les travailleurs.

Les valeurs des VA (3,83 à 5,87 L/min) et des Q (4,04 à 6,73 L/min) qui sont habituellement utilisées lors d'études pharmacocinétiques à base physiologique (PCBP) correspondent à des mesures pour des sujets au repos (Arms et Travis 1988; USEPA 1988; Travis et Hattemer-Frey 1991; Krishnan et Andersen 2001; Haddad *et al.* 2006; Valcke et Krishnan 2009). L'étude de Price *et al.* (2003) a le mérite d'être la seule publication à avoir tenté d'estimer les valeurs des VA et des Q en fonction de l'âge des individus pour des fins de modélisation PCBP. Par contre, les VA et les Q de Price *et al.* (2003)

correspondent encore une fois à des valeurs centrales sans écart-type pour des sujets au repos (couchés ou assis). Les mesures de Lees *et al.* (1967) pour des enfants sous sédation (suite à l'ingestion d'un mélange de mépéridine, de thorazine et de phénergan) ont contribué à biaiser les VA des enfants âgés de 3 à 6 mois. Le nombre très limité de mesures dans Price *et al.* (2003) biaise également la solidité statistique de l'ordre de grandeur des VA et Q pour chaque âge. Par exemple, les valeurs de Q pour les individus de 5 à 52 ans proviennent uniquement de 26 mesures publiées dans Cayler *et al*. (1963), tandis que celles des VA pour les individus de 5 à 18 ans sont basés sur les 54 mesures rapportées par Kerr (1976).

La valeur de VA varie en fonction de celles de VE et du ratio de l'espace mort physiologique sur le volume courant des sujets (Guyton 1991); au même titre que Q, les valeurs de ces trois paramètres varient 1) lorsque les individus en position horizontale (couchée) se redressent en position verticale (assise ou debout) et 2) lorsqu'ils effectuent des efforts physiques (West 1962; Damato *et al.* 1966; Malmberg 1966; Stenberg *et al.* 1967; Craig *et al.* 1971; Hossack et Bruce 1982; Miyamoto *et al.* 1983; Hopkins *et al.* 2000). Les individus sont également beaucoup plus susceptibles d'être exposés aux différents polluants environnementaux durant l'ensemble des activités de la journée que lors de repos. Ils sont évidemment moins à risque durant leur sommeil. Les valeurs de VA et de Q utilisées actuellement pour des individus au repos lors d'études de modélisation PCBP contribue donc à sous-estimer l'ordre de grandeur des doses internes en xénobiotiques environnementaux et en métabolites estimés. Par ailleurs, les valeurs moyennes, les écart-types et les distributions des centiles des valeurs des VA et Q pour l'ensemble des activités de la journée des individus en fonction de l'âge n'ont jamais été déterminés dans la littérature.

De ce qui précède, on peu conclure qu'il existe encore beaucoup d'inconnues en ce qui a trait à la valeur des paramètres cardio-pulmonaires, notamment à ceux utilisés pour des fins d'études PCBP, qu'il s'agisse des valeurs centrales (moyennes et médianes) ou qu'il s'agisse des distributions statistiques de ces valeurs centrales, et ceci, notamment pour l'ensemble des activités quotidiennes des sujets en fonction de l'âge.

1.5 PISTES DE SOLUTION A LA PROBLEMATIQUE ACTUELLE

1.5.1 Élément clé de la détermination des TQI, des VE, des VA et des Q

Le processus aérobie assure la combustion des composantes des diètes alimentaires durant la phase postprandiale (protéines, lipides, carbohydrates) et celle des métabolites durant la phase de jeûne (glucose, glycogène, acide hydroxy-3 butyrique, acide acétoacétique, triacylglycérol) afin de générer la quasi-totalité de l'énergie nécessaire aux activités métaboliques cellulaires (Durnin et Passmore 1967; Layton 1993; Elia 1997). Durant ce processus, l'oxygène (O_2) est consommé, tandis que de l'énergie, du dioxyde de carbone (CO_2) et de l'eau sont générés (Durnin et Passmore 1967). Le processus de la respiration assure la captation de l'O_2 de l'air ambiant, d'une part, et l'exhalation du CO_2, de l'excédant d'O_2 et des vapeurs d'eau, d'autres part (Guyton 1991). Une fraction du volume VT (donc du VE) participe à l'échange gazeux et constitue le volume du VA, comparé au volume restant qui est exhalé et communément appelé l'espace mort Bohr-Enghoff (VDphys) ou encore l'espace mort physiologique (Guyton 1991). Le VDphys inclut le volume de l'espace respiratoire, connu sous le terme d'espace mort anatomique, ainsi que le volume des alvéoles non fonctionnelles non perfusées, connu sous le terme d'espace mort alvéolaire (Guyton 1991). Le lien entre le VA, le VE (en L/min) et les volumes VDphys et VT (en L) est bien connu et il est exprimé sous la forme des équations suivantes (Guyton 1991):

$$VA = (VT - VDphys) \times fr$$ Équation 15

$$VA = VE \times \left[1 - \frac{VDphys}{VT}\right]$$ Équation 16

où :

VDphys = espace mort physiologique (L);

À partir des alvéoles fonctionnelles, l'O_2 se fixe à la déoxyhémoglobine et se diffuse à travers le sang artériel. L'O_2 est extrait de l'oxyhémoglobine et est livré aux cellules pour consommation jusqu'à ce que sa pression partielle locale (PO_2) dans les capillaires soit insuffisante pour lui permettre une diffusion passive à travers les tissus (Guyton 1991). L'excès d'O_2 et le CO_2 produit au niveau cellulaire qui se retrouvent dans le sang veineux sont exhalés par les poumons. La valeur de Q (en L de sang/min) varie en fonction de la fréquence cardiaque et du volume de propulsion cardiaque selon la relation suivante (Guyton 1991):

$$Q = VP \times fc$$ Équation 17

où :

VP = volume propulsé après chaque battement cardiaque (L de sang);

fc = fréquence cardiaque (nombre de battements cardiaques/minute).

L'ensemble des liens entre VO_2, Q (en L/min) et les contenus artériel et veineux en oxygène se résume par l'équation de Fick (1870) :

$$VO_2 = Q \times (CaO_2 - CvO_2) \qquad \text{Équation 18}$$

où :

CaO_2 = contenu artériel en oxygène (ml d'O_2/ml de sang);

CvO_2 = contenu veineux en oxygène (ml d'O_2/ml de sang);

La différence artérioveineuse en oxygène (c.-à-d. CaO_2-CvO_2, abrégée DAVO, en ml d'O_2/ml de sang) correspond à l'O_2 extrait de l'oxyhémoglobine et transféré aux cellules pour consommation.

Ainsi, on peut conclure que le ralentissement ou l'accélération des processus respiratoires et cardiovasculaires, donc les fluctuations des valeurs de VO_2, VE, VA, Q durant la journée et de TQI (VE sur 24 heures) sont fonction des demandes en énergie, c'est-à-dire, plus spécifiquement, de la dépense d'énergie. La dépense d'énergie des individus devient ainsi un élément clé pour la détermination des valeurs des paramètres cardio-pulmonaires et des TQI. La mesure la plus précise de cette dépense d'énergie (Torun 1996; Stifelman 2007) s'effectue par la méthode du double marquage isotopique des molécules d'eau (DMIME).

1.5.2 Méthode du double marquage des molécules d'eau

La méthode du DMIME implique systématiquement la mesure de deux types de dépenses énergétiques chez les mêmes sujets (IOM 2002): la dépense énergétique quotidienne totale (DEQT) et le taux métabolique de base (TMB). Le TMB est mesuré par calorimétrie indirecte chez les sujets au repos à jeun depuis 12 à 13 heures et au réveil (Guyton 1991).

Le TMB correspond alors à la somme des dépenses minimales d'énergie nécessaires pour maintenir les individus en vie (Guyton 1991). Les valeurs des TMB (en kcal/min) sont par la suite exprimées sur une base de 24 heures en dépense énergétique quotidienne de base (DEQB en kcal/jour). Ces sujets ingèrent par la suite des doses connues de deux isotopes de l'eau ($H_2{}^{18}O$ et ${}^2H_2O$). Durant le protocole analytique, d'une durée qui varie de 7 à 21 jours, les sujets vaquent librement à leur occupation sans aucune restriction. Les mesures des taux d'élimination du deutérium (${}^2H$) et d'oxygène lourd-18 (${}^{18}O$) dans les prélèvements d'urine ou de salive par spectrométrie de masse permettent le calcul des dépenses énergétiques quotidiennes totales (DEQT) chez ces sujets (IDECG 1990).

La valeur de chaque DEQT englobe l'ensemble de l'énergie qui a été dépensée par un sujet, minute par minute, 24 heures par jour, durant 7 à 21 jours (IDECG 1990). Chaque DEQT en kcal/jour peut donc être convertie en TQI en m^3/jour en faisant intervenir les valeurs de H et de VQ (Brochu *et al.* 2006c). Compte tenu que les valeurs de DEQT et de DEQB ont été mesurées chez les mêmes sujets, une opération de soustraction (c.-à-d. DEQT-DEQB) permet d'obtenir la dépense d'énergie nécessaire pour exécuter les activités durant la journée. Ces données peuvent donc être utilisées pour calculer les valeurs des VE, VA et des Q pour ces sujets. Les poids corporels et les grandeurs qui sont également systématiquement mesurés chez les mêmes sujets par la méthode du DMIME (IDECG 1990) permettent les calculs précis des paramètres cardio-pulmonaires et des TQI par unité de poids corporel (en kg) et de surface corporelle (en m^2). Enfin, les quelques milliers de mesures individuelles du DMIME qui sont disponibles dans la littérature pour des sujets de tous âges permettent des calculs statistiques précis (IOM 2002).

1.5.2.1 *Mesures par calorimétrie indirecte*

La calorimétrie indirecte permet de déterminer les dépenses d'énergie des sujets au repos ou lors d'exercices par la mesure simultanée de leur VO_2 et de leur taux de production de bioxyde de carbone (VCO_2) à STPD, le tout complété par la mesure d'excrétion d'azote urinaire (Durnin et Passmore 1967). Lors de la détermination du TMB, les échanges gazeux sont mesurés pendant une période de 40 minutes immédiatement au réveil (Guyton 1991). La dépense d'énergie est calculée à partir des mesures de VO_2, de VCO_2 (en L/min) et d'excrétion d'azote urinaire (gramme) en utilisant l'équation de Weir (1949):

$$E = 3{,}941 \times VO_2 + 1{,}106 \times VCO_2 - 2{,}17 \times N$$ Équation 19

La précision des mesures de dépenses énergétiques obtenues par calorimétrie indirecte et l'équation de Weir (1949) a été déterminée en chambre hermétique (calorimètre) comme variant entre 0,6 à 0,7% lorsque les mesures d'excrétion d'azote urinaire sont incluses dans les calculs afin de tenir compte du métabolisme des protéines (Turell et Alexander 1963). Par ailleurs, l'exactitude des dépenses énergétiques a été mesurée comme variant de +1 à +2% lorsque les calculs ne tiennent pas compte des mesures d'excrétion d'azote urinaire, donc lorsque N dans l'équation 19 est égale à zéro (Turel et Alexander 1963).

1.5.2.2 *Mesures spectrométriques des taux d'élimination des isotopes de l'eau*

L'anhydrase carbonique des érythrocytes catalyse la combinaison du CO_2 avec l'eau pour former de l'acide carbonique (H_2CO_3) lequel se transforme rapidement en ions bicarbonates (HCO_3^-). Cet enzyme catalyse la réaction inverse au niveau des poumons pour permettre l'exhalation de CO_2 (Figure 1; Guyton 1991)

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow HCO_3^- + H^+$$ Équation 20

Une portion des doses ingérées des isotopes de l'eau ($H_2{}^{18}O$ et ${}^2H_2O$) durant la méthode du DMIME réagit avec le CO_2 pour former de l'acide carbonique isotopique qui se transforme rapidement en ions bicarbonates isotopiques : ${}^2HCO_3^-$ et $HC^{18}OO_2^-$ (Figures 2 et 3; IDECG 1990). Ces ions quittent les érythrocytes afin d'être transportés dans le plasma jusqu'au niveau des alvéoles. La réaction inverse a alors lieu dans les érythrocytes. Le ${}^2H$ des ions ${}^2HCO_3^-$ se retransforme en ${}^2H_2O$ (Figure 2), tandis qu'une portion du ${}^{18}O$ des ions $HC^{18}OO_2^-$ retourne dans la molécule d'eau isotopique ($H_2{}^{18}O$), alors que l'autre portion se transforme en bioxyde de carbone isotopique : $C^{18}O_2$ (Figure 3). C'est donc un mélange de bioxyde de carbone non isotopique (CO_2) et isotopique ($C^{18}OO$) qui se retrouve exhalé (Figure 3). La mesure du taux d'élimination du deutérium dans l'organisme reflète ainsi la perte d'eau, tandis que celui de l'oxygène lourd-18 reflète la perte d'eau et le taux de production de CO_2 qui est exhalé. La différence entre le taux d'élimination de deutérium (${}^2H$) et celui de l'oxygène lourd-18 (${}^{18}O$) dans les urines ou la salive permet de calculer la valeur moyenne du VCO_2 pour des périodes de 7 à 21 jours (IDECG 1990; Brochu *et al.* 2006c).

La combustion d'un gramme de lipides, de protéines et de carbohydrates requiert des volumes de consommation d'oxygène de 2,013, 0,957 et de 0.746 Litres et de production de CO_2 de 1,431, 0,774 et 0,746 Litres, respectivement. Les ratios d'échanges respiratoires VCO_2/VO_2 (RER) sont donc de 0.711, 0,809 et de 1,000 (sans unité) pour ces nutriments, respectivement (Durnin et Passmore 1967 ; Guyton 1991). L'analyse de la diète alimentaire des individus durant la période de l'étude du DMIME permet donc de calculer le RER. Le RER peut également être calculé selon les mesures des VO_2 et des VCO_2 en chambre hermétique ou par calorimétrie indirecte (Durnin et Passmore 1967 ; Guyton

1991). La valeur du RER (c.-à-d. VCO_2/VO_2) permet de calculer le VO_2 qui est associé au VCO_2 mesuré par le double marquage des molécules d'eau. Ces VO_2 et VCO_2 sont par la suite convertis en DEQT (kcal/jour) en utilisant l'équation de Weir (équation 13).

La précision moyenne des mesures de DEQT obtenues par le DMIME ont été déterminées comme variant de -1,0 à +3,3% lorsque la source habituelle d'eau potable n'est pas modifiée (IDECG 1990). Durant la mesure du DMIME, les sujets sont avisés de ne pas modifier leur source habituelle d'eau potable, un tel changement générant une erreur moyenne sur les DEQT de -8,7% chez des enfants en bas âge et de +5,3% chez des adultes (DECG 1990).

1.6 OBJECTIFS DE LA THESE

L'objectif global a pour but de démontrer la possibilité de déterminer des taux quotidiens d'inhalation (TQI) et des paramètres cardio-pulmonaires chez l'humain en utilisant les données de la littérature en rapport au double marquage isotopique des molécules d'eau (DMIME) pour l'analyse du risque. Des données individuelles tirées de la littérature qui sont systématiquement mesurées chez les mêmes sujets par la méthode du DMIME seront utilisées dans le cadre de cet objectif. Il s'agit ici de la dépense énergétique quotidienne de base (DEQB), la dépense énergétique quotidienne totale (DEQT), le poids corporel et la grandeur. Les DEQT obtenues par le DMIME correspondent aux mesures les plus précises des dépenses d'énergie des individus sur 24 heures selon l'état actuel des connaissances (IDECG 1990).

Le premier objectif (voir Article I – Brochu *et al.* 2006a) a pour but de développer une méthodologie beaucoup plus précise que les approches actuelles et qui sera basée sur les DEQT pour déterminer les valeurs moyennes, les écart-types et les centiles des TQI (en m^3/jour et en m^3/kg-jour) en fonction de l'âge des individus âgés de 1 mois à 96 ans. Cette cohorte de sujets inclura des individus de poids corporel normal, des sujets présentant un problème de poids et des adultes dont le mode de vie exige des dépenses d'énergie au-delà de l'ordinaire.

Le deuxième objectif (voir Article II – Brochu *et al.* 2006b) prévoit l'adaptation de la nouvelle procédure basée sur le DMIME pour calculer les moyennes, les écart-types et les centiles des TQI (en m^3/jour et en m^3/kg-jour) pour les adolescentes et les femmes enceintes et en lactation âgées de 11 à 55 ans de faibles poids corporels, de poids normaux et pour celles souffrants d'embonpoint et d'obésité. L'analyse des valeurs des TQI obtenues dans le deux premiers articles (Brochu *et al.* 2006a, 2006b) permettra d'identifier les sujets qui inhalent le plus d'air par unité de poids corporel (en m^3/kg-jour), donc ceux qui inhalent le plus de polluants de l'air pour des concentrations d'exposition données.

Le troisième et le quatrième objectifs (Articles III et IV) visent à exploiter la précision des valeurs des DEQB (+1 à +2%) et des DEQT (–1,0 à +3,3%) obtenues par la méthode du DMIME afin de calculer des valeurs de TQI (troisième objectif) et des paramètres cardio-pulmonaires pour l'ensemble des activités de la journée (quatrième objectif) chez des individus de poids corporel normal. Les paramètres cardio-pulmonaires incluent les taux de ventilation minute (VE), les taux de ventilation alvéolaire (VA), les débits cardiaques (Q) et les ratios de ventilation-perfusion (VA/Q). Les valeurs moyennes, les écart-types et les centiles des TQI (troisième objectif) seront calculées pour des individus âgés de 2,6 mois à 96 ans (en m^3/jour, m^3/kg-jour et m^3/m^2-jour), tandis que celles des VE, VA et Q (en L/min, L/kg-min et L/m^2/min) et VA/Q (sans unité) seront déterminées pour des sujets âgés de 5 à 96 ans (quatrième objectif).

1.7 DEMARCHE METHODOLOGIQUE ET ORGANISATION DE LA THESE

Le développement d'une nouvelle méthode pour déterminer les TQI selon l'approche du DMIME fera l'objet de l'Article I. Cette étape implique : i) le calcul du volume d'oxygène consommé par kcal d'énergie dépensée durant la phase postprandiale (H_P en L de O_2/kcal) en fonction de la diète alimentaire des Canadiens (comparativement à la valeur spécifique aux Américains), ii) la détermination du coût énergétique de la croissance (CEC) des individus de la naissance à l'état adulte, et iii) la modification à apporter à l'équation 10 afin d'exprimer les TQI en fonction des valeurs de DEQT, des CEC, des équivalents ventilatoires (VQ) et de H_P. Cette nouvelle méthode permettra de calculer les fluctuations des TQI selon les différentes catégories de sujets de la population (n=2197). Les valeurs moyennes, les écart-types et les centiles des TQI (en m^3/jour et en m^3/kg-jour) seront calculées pour i) les nouveau-nés âgés de 1 mois nourris au lait maternisé (préparations lactées commerciales) et ceux nourris au sein (n=20), ii) les sujets masculins et féminins de poids corporel normal âgés de 2,6 mois à 96 ans (n=1252), iii) les individus souffrant d'embonpoint ou d'obésité âgés de 4 à 96 ans (n=679), iv) les adultes sous-alimentés ou anorexiques (n=76) et, v) ceux (n=170) dont le mode de vie exige des DEQT au-delà de l'ordinaire (athlètes, explorateurs, soldats). Les valeurs des TQI des nouveau-nés ayant des faibles poids corporels âgés de 3 semaines (n=11) seront également déterminées en utilisant les DEQT calculées selon les bilans nutritionnels (ingestion et excrétion) effectués durant une période de 3 jours. Les TQI calculés pour des adultes anorexiques et des individus souffrant de surplus de poids âgés de 4 à 96 ans seront comparés à ceux des groupes de sujets en santé d'un même sexe et d'âge relativement semblable.

Une deuxième étape consiste en la détermination des moyennes, des écart-type et des centiles des TQI (en m^3/jour et en m^3/kg-jour) pour les adolescentes et les femmes âgées de 11 à 55 ans (n=357) de poids corporel normal, inférieur ou supérieur aux valeurs normales durant leur 9^e, 22^e et 36^e semaine de grossesse et leur 2^e, 6^e et 27^e semaine de lactation (Article II). Ces valeurs des TQI seront comparées à celles d'adolescents et d'hommes de poids corporel normal âgés de 11 à 55 ans, ainsi qu'à celles d'adolescentes et de femmes non-enceintes et non-allaitantes du même âge. Ces calculs nécessitent la détermination des valeurs de VQ et des coûts énergétiques durant les 9^e, 22^e et 36^e semaines de la gestation (CEG) et durant les 2^e, 6^e et 27^e semaines de la lactation (CEL). Les valeurs du CEL seront calculées en tenant compte des coûts énergétiques de la synthèse du lait maternel et du transfert d'énergie au nouveau-né. Les CEG, les CEL et les valeurs de VQ seront intégrés dans l'équation développée dans l'Article I pour calculer les TQI. Les valeurs des TQI de l'Article II pour les femmes enceintes et pour celles qui allaitent n'ont jamais été publiées à ce jour. Il en est de même pour les TQI des différentes catégories de sujets qui auront été calculés dans le cadre de l'Article I. L'analyse des ces valeurs permettra l'identification des individus de la population qui inhalent le plus d'air par unité de poids corporel (m^3/kg-jour), donc ceux qui inhalent le plus de polluants de l'air (en µg/kg-jour) pour une concentration donnée d'exposition.

La troisième partie de la thèse (Article III) consiste en la détermination des moyennes et des écart-types des paramètres respiratoires de nuit (H_J pour les sujets à jeun, VQβ pour les sujets au repos) et de jour (H_P postprandial, VQα pour l'ensemble des activités de la journée) et leur intégration avec les valeurs des DEQB et des DEQT du DMIME dans le processus de calcul des TQI. Cette détermination des moyennes et des écart-types de H et de VQ permettra d'optimiser la précision des distributions des centiles des TQI. Ce volet nécessite au préalable une importante cueillette de données de la littérature chez des sujets en santé au repos et/ou en situation d'exercice. Les facteurs pris en compte seront : i) les diètes alimentaires de sujets de 17 pays différents et les valeurs des taux de consommation d'oxygène (VO_2) et de production de bioxyde de carbone (VCO_2) mesurées simultanément chez des individus de tous âges, ceci dans le but d'analyser les possibles fluctuations des valeurs de H_J et de H_P, ii) les valeurs de VE et de VO_2 mesurées simultanément chez des sujets de tous âges, ceci dans le but d'étudier les facteurs qui affectent la variations des valeurs de VQβ et de VQα et iii) la durée des périodes de sommeil (Sld) chez les individus en fonction de l'âge. L'analyse critique de l'ensemble de ces données guidera dans l'élaboration d'une procédure de sélection des données nécessaires au calcul des valeurs de H_J, H_P, VQβ et de VQα reflétant plus adéquatement la réalité biologique des individus. Comparativement à la procédure connue (Layton 1993) basée sur le calcul des contributions en protéine, en lipides et en carbohydrates des diètes alimentaires, l'Article III innovera, en plus, par le fait que les valeurs de H_J et H_P seront calculées en incorporant dans l'équation de Weir (équation 13) les mesures de VO_2 et de VCO_2 tirées de la littérature. Les valeurs de H_J, de H_P, de VQβ, de VQα et de Sld seront intégrées avec les valeurs de DEQB, de DEQT et de CEC (Article I) dans une nouvelle équation afin de calculer les valeurs des TQI (moyennes, écart-types et centiles en m^3/jour,

m^3/kg-jour et m^3/m^2-jour) pour les individus de poids corporel normal âgés de 2,6 mois à 96 ans (n=1235).

La quatrième étape (Article IV) consiste en la détermination des paramètres physiologiques et cardio-pulmonaires propres à l'ensemble des activités de la journée des sujets de poids corporel normal âgés de 5 à 96 ans (n=902). La procédure qui aura été élaborée dans l'Article III pour la sélection des données utiles au calcul des VQα sera utilisée pour identifier celles nécessaires au calcul des valeurs des DAVOα (en ml de O_2/ml de sang) et des ratios VDphysα/VTα (sans unité) pour l'ensemble des activités de la journée des sujets. Des conditions additionnelles de sélection des données en rapport avec les DAVO devront être déterminées via la collecte et l'analyse de données complémentaires pertinentes (Q, et DAVO pour différents VO_2). Des équations physiologiques devront être modifiées (c.-à-d. équations 10, 16 et 18) afin d'exprimer les valeurs de E, VO_2, VE, VA et Q en fonction des valeurs de CEC de l'Article I, des Sld de l'Article III, avec celles des DEQB, DEQT et selon le cas selon l'une ou plusieurs des valeurs suivantes : H_P, VQα, DAVOα et VDphysα/VTα. Comparativement aux moyennes, écart-types et centiles des ratios VA/Q (sans unité), celles de E (kcal/min), de VO_2 (L d'O_2/min), des Q (L de sang/min), des VE et des VA (L d'air/min) qui seront déterminées dans le cadre de l'Article IV seront également exprimées par unité de poids corporel (par kg) et par unité de surface corporelle (par m^2). On ne retrouve pas dans la littérature actuelle une telle série de données pour des sujets âgés de 5 à 96 ans (Eα, VO_2α, VEα, Qα, DAVOα, VAα/Qα, VDphysα/VTα et VAα).

Les valeurs des TQI des Articles I, II, III et IV seront basées sur des DEQT qui reflètent l'oxygénation adéquate de divers groupes d'individus (356 à 2197) vaquant librement à leur occupation pendant des périodes globales respectives de plus de 30 000, 6 000, 19 000 et 14 000 journées. En plus de tenir compte de mesures du DMIME qui n'ont jamais été exploitées en toxicologie et ni en analyse du risque, les Articles I à IV prendront en compte les connaissances actuelles sur les principes et méthodes de la toxicologie et celles qui sont propres à la physiologie et la physiopathologie. L'analyse des données impliquera par moment l'utilisation de tests statistiques. Les simulations de Monte Carlo permettront d'intégrer les écart-types dans les processus de calculs des distributions des centiles des TQI, des paramètres cardio-pulmonaires (VEα, Qα, VAα, VAα/Qα) et des paramètres complémentaires (Eα, $VO_2\alpha$, H_J, H_P, VQβ, VQα, DAVOα, VDphysα/VTα).

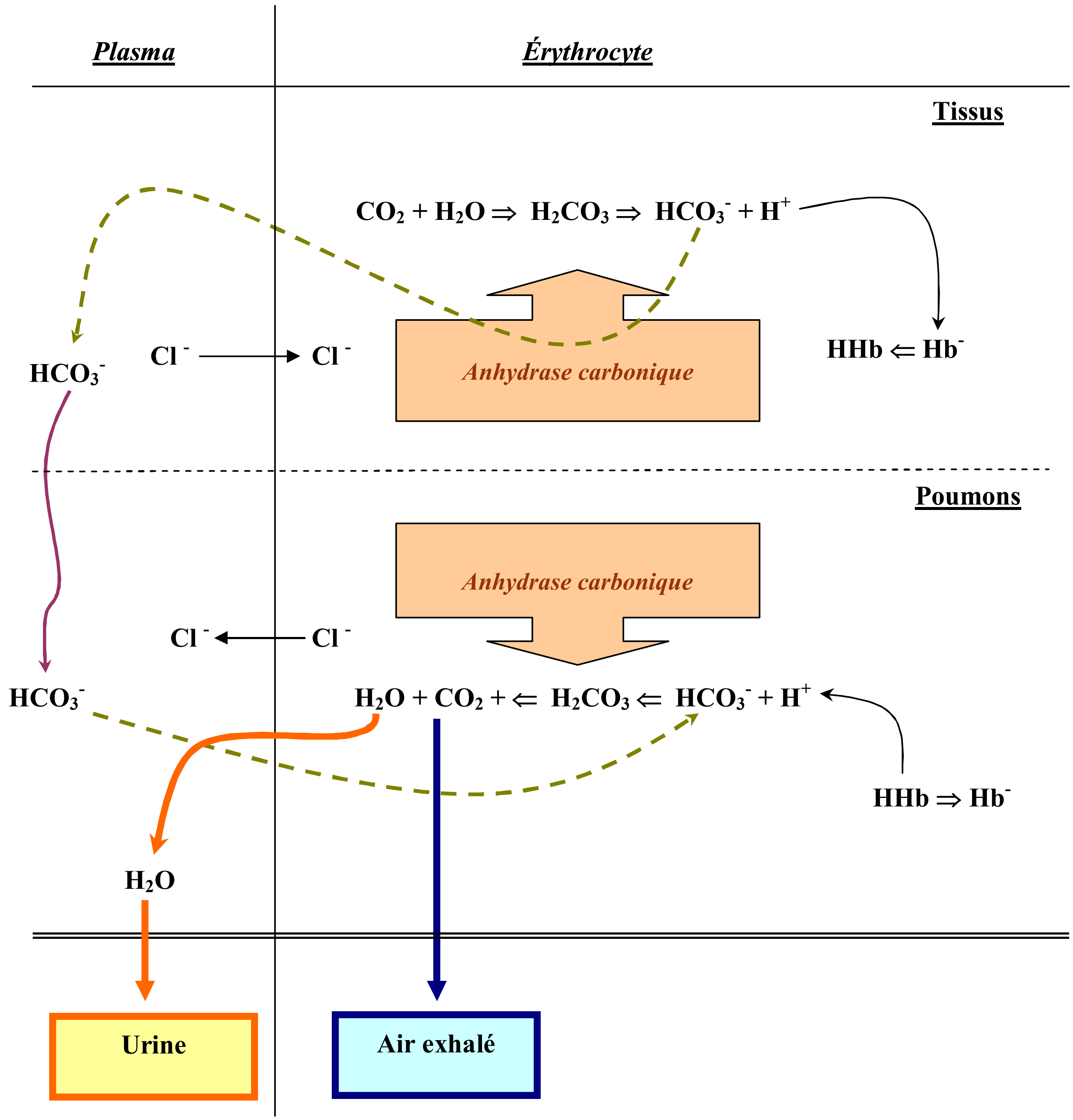

Figure 1 **Métabolisme du bioxyde de carbone et de l'eau via l'ion bicarbonate (Hb : hémoglobine)**

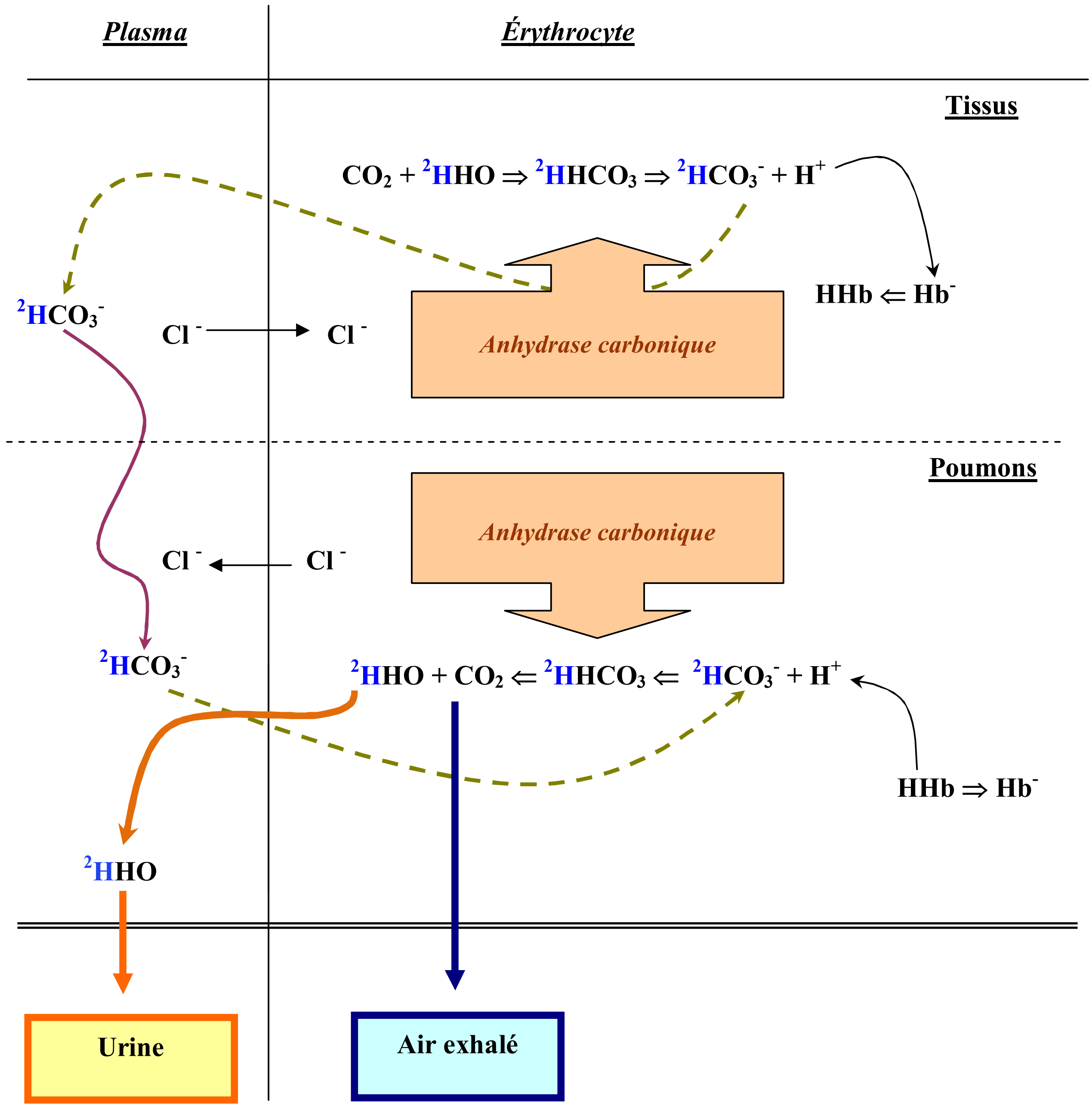

Figure 2 Métabolisme du bioxyde de carbone et de l'eau isotopique (^{2}HHO) via l'ion bicarbonate (Hb : hémoglobine)

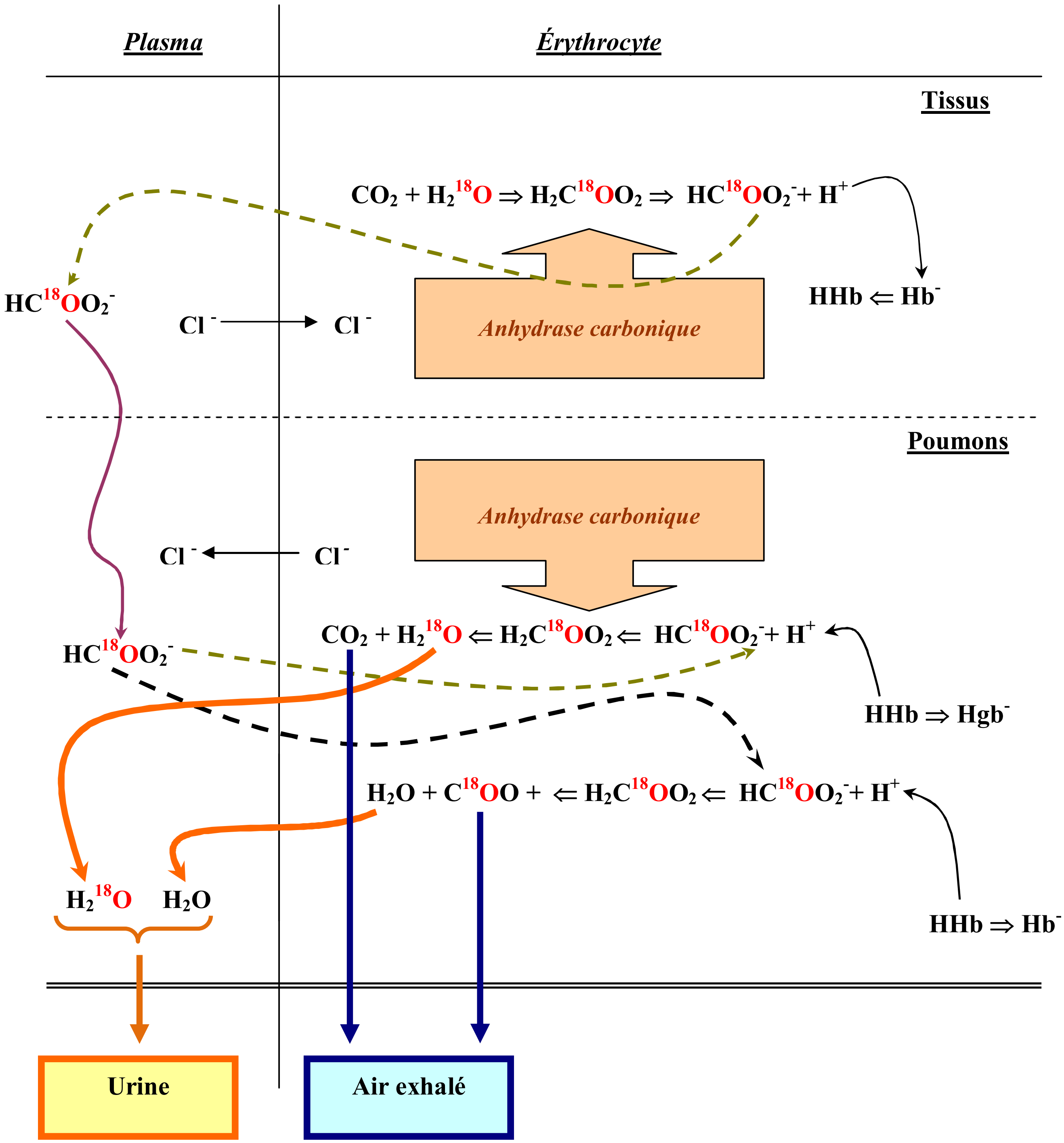

Figure 3 **Métabolisme du bioxyde de carbone et de l'eau isotopique ($H_2{}^{18}O$) via l'ion bicarbonate (Hb : hémoglobine)**

CHAPITRE DEUXIÈME :

2 Article I

Physiological daily inhalation rates for free-living individuals aged 1 month to 96 years, using data from doubly labeled water measurements: a proposal for air quality criteria, standard calculations and health risk assessment

PHYSIOLOGICAL DAILY INHALATION RATES FOR FREE-LIVING INDIVIDUALS AGED 1 MONTH TO 96 YEARS, USING DATA FROM DOUBLY LABELED WATER MEASUREMENTS:

A PROPOSAL FOR AIR QUALITY CRITERIA, STANDARD CALCULATIONS AND HEALTH RISK ASSESSMENT

Pierre Brochu[1, 2, 3], Jean-François Ducré-Robitaille[1] and Jules Brodeur[2]

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[1] Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi et de l'état de l'environnement, Service des avis et expertises scientifiques, gouvernement du Québec, édifice Marie-Guyart, 7e étage, 675, boulevard René-Lévesque Est, Québec, QC, G1R 5V7, Canada.

[2] Département de santé environnementale et santé au travail, Faculté de médecine, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, QC, H3C 3J7, Canada.

[3] To whom all correspondence should be addressed.

ABSTRACT

Reported disappearance rates of oral doses of doubly labeled water (^2H_2O and $H_2{}^{18}O$) in urine, monitored by gas-isotope-ratio mass spectrometry for an aggregate period of over 30,000 days and completed with indirect calorimetry and nutritional balance measurements, have been used to determine physiological daily inhalation rates for 2210 individuals aged 3 weeks to 96 years. Rates in m^3/kg-day for healthy normal-weight individuals (n=1252) were higher by 6 to 21% compared to their overweight/obese counterparts (n=679). Rates for healthy normal-weight males and females drop by about 66 to 75% within the course of a lifetime. Infants and children between the age of 3 weeks to less than 7 years inhale 1.6 to 4.3 times more air (0.395 ± 0.048 to 0.739 ± 0.071 m^3/kg-day, mean ± S.D., n=581) than adults aged 23 to 96 years (0.172 ± 0.037 to 0.247 ± 0.039 m^3/kg-day, n=388). The 99th percentile rate of 0.725 m^3/kg-day based on measurements for boys aged 2.6 to less than 6 months is recommended for air quality criteria and standard calculation for non-carcinogenic compounds pertaining to individuals of any age or gender (normality confirmed using the Shapiro-Wilk test, $p \geq 0.05$). This rate is 2.5 fold more protective than the daily inhalation estimate of 0.286 m^3/kg-day published by the Federal Register in 1980 (i.e. 20 m^3/day for a 70-kg adult). It ensures that very few newborns aged 1 month and younger, less than 1% of infants aged 2.6 to less than 6 months and of course no older individuals up to 96 years of age inhale more toxic chemicals than associated safe doses which are not anticipated to result in any adverse effects in humans, when air concentration reaches the resulting air quality criteria and standard values. This rate is also protective for underweight, overweight and obese individuals. Finally, as far as newborns are concerned, a rate of 0.956 m^3/kg-day based on the 99th percentile estimates is recommended for short-term criteria and standard calculations for toxic chemicals that yield adverse effects over instantaneous to short-term duration.

Key words: daily inhalation rates, distribution percentiles, probability density functions, air quality criteria, standard value, risk assessment, doubly labeled water.

LIST OF MAIN ABBREVIATIONS

BEE: basal energy expenditure (BMR expressed on a 24-hour basis)

BMI: body mass index

BMR: basal metabolic rate (punctual measurement)

DLW: doubly labeled water

DMET: daily metabolic equivalent (TDER/BEE ratio)

ECG: stored daily energy cost for growth

H: oxygen uptake factor, volume of 0.21 L of oxygen (at standard temperature and pressure, dry air) consumed to produce 1 kcal of energy expended

MET: metabolic equivalent (BMR multiplier)

TDEE: total daily energy expenditure

TDER: total daily energy requirement (summation of ECG and TDEE)

V_E: minute volume rate

VO_2: oxygen uptake rate

VQ: ventilatory equivalent ratio (V_E at body temperature pressure saturation/VO_2 at standard temperature and pressure, dry air)

INTRODUCTION

Human short- and long-term adverse health effects are well known to occur as a result of exposure to air pollutants (Abbey *et al.* 1993; Burnett *et al.* 1994, 1997a, 1997b, 1997c; Coyle *et al.* 2003; Ghio and Devlin 2001; Godleski *et al.* 2000; Hajat *et al.* 2001; Heinrich, *et al.* 1999; Liu *et al.* 2003; Neher and Koenig, 1994; Pope, 2000; Schwartz *et al.* 1991; Tolbert *et al.* 2000; Ware *et al.* 1993; Yang *et al.* 2003). Several studies have also provided persuasive evidences that air pollution is directly linked to mortality (Abbey *et al.* 1999; Burnett *et al.* 1998a, 1998b, 2000, 2001; Dockery *et al.* 1993; Godleski *et al.* 2000; Loomis *et al.* 1999; Pope *et al.* 2002, 2004; Samet *et al.* 2000; Thurston and Ito 2001; Villeneuve *et al.* 2003; Ware 2000). Chronic adverse health effects have been reported even at relatively low levels of particulate air pollutants currently measured in urban areas (Bascom *et al.* 1996a, 1996b). Precise daily inhalation rates are essential in health risk assessment, since lung ventilation controls the transportation of air pollutants to the respiratory tract and influences their deposition onto surfaces of the conducting airways and pulmonary region, and ultimately determine the inhaled doses of air pollutants (Polgar and Weng 1979). Although numerous lung function measurements, notably minute ventilation rates, have been taken from subjects performing various tasks, there have been no experimental measurements of the physiological 24-hour inhalation rates of free-living people (Allan and Richardson 1998; Layton 1993). In the United States, the value of 20 m^3/day for a 70-kg adult based on an 8-hour work day has been adopted as a standard inhalation rate for humans (Federal Register, 1980). This value is widely used to determine the inhaled dose for a given air pollutant for adults and it is notably used in the default approach for the determination of reference concentrations (Benson *et al*. 2002; Paustenbach 2001; USEPA 1991, 1996; Versar 1989). In Canada, a daily inhalation rate of 23 m^3/day was derived from the inhalation data determined by the International Commission on Radiological Protection (Health Canada 1994; Snyder *et al.* 1975).

Respiratory symptoms and lung function changes are the most common effects resulting from air pollution, particularly in children (Braun-Fahrländer *et al.* 1997; Brunekreef *et al*. 1997; Chen *et al.* 1998; Dockery *et al*. 1989, 1996; Hoek *et al.* 1990; Hoelzer *et al.* 2002; Jedrychowski and Flak 1998; Peters *et al.* 1999; Wjst *et al.* 1993). For instance, ambient concentrations of ozone were positively associated with respiratory hospital admission among young children and the elderly in Vancouver, British Columbia (Yang *et al.* 2003). Notably, air pollution was positively associated with the prevalence of asthma in children and adults (Gielen *et al.* 1997; Guo *et al.* 1999; Hales *et al.* 1998; Norris *et al.* 1999; Peters *et al.* 1997; Segala *et al.* 1998; Sheppard *et al.* 1999; Studnicka *et al.* 1997; Sunyer *et al.* 1997; Tolbert *et al.* 2000). Functional signs of airway obstruction and obstructive pulmonary disease have also been linked to air pollution (Sunyer *et al.* 1991; Zapletal *et al.* 1976). In order to estimate intake and uptake variations of air pollutants as a function of age from infancy to adulthood, age dependent daily inhalation rates have rapidly become essential in health risk assessment. Two types of approaches have been developed for this purpose: time-activity-ventilation and metabolic energy conversion (Allan and Richardson 1998; Finley *et al.* 1994; Layton 1993; Roy and Courtay 1991; Versar 1989). In the first approach, inhalation rates are estimated by taking into account the cumulative minute ventilation rates (in L/min) associated with activities or levels of activity and their duration throughout the day (e.g., sleeping, walking). In the second approach, inhalation estimates are based on the daily food-energy intake or cumulative energy expenditure (in kcal/min) required to support activities or levels of activity throughout the day. A critical review of relevant biases and magnitude of under- and overestimations for each approach appears in a companion paper by Brochu *et al.* (2006a), where it is shown that daily inhalation rates resulting from such bases are partially biased, notably by lack of data and adequate statistical values for some age/sex groups and activity levels.

Monte Carlo simulations have been used by Allan (1995) to estimate 24-hour inhalation rate probability density functions for use in health risk assessment by the Health Protection Branch of Health Canada (Allan and Richardson, 1998). These Monte Carlo simulations as well as those conducted by Finley *et al.* (1994) to estimate statistical distributions for daily inhalation rates do not eliminate the biases from the preliminary input breathing parameters, as they include them in the statistical process (Brochu *et al.* 2006a). In fact, accuracy of daily inhalation estimates has been improved by conversion of daily food-energy intakes from dietary surveys as done by Layton (1993). The resulting inhalation values consist of single values (point estimates) for each age group without standard deviations and percentile distributions associated to each sub-group of individuals. Yet, the daily inhalation rates for individuals aged less than 1 year up to 18 years were recommended in United States as long-term inhalation rates and for long-term dose assessment of air pollutants (USEPA, 1997; Versar, 2000). Many other biases are present, in particular in self-reported dietary intakes during food surveys (Bandini *et al.* 1990a, 1990b, 2003; Bellisle, 2001; Black *et al.* 1993; Johnson 2000; Livingston *et al.* 1990; Subar *et al.* 2003; Trabulsi and Schoeller 2001; Torun *et al.* 1996). Moreover, energy loss in stool, intestinal gases and urine has not been subtracted from dietary energy intakes reported by Layton (1993) before converting metabolic energy into daily inhalation rates (IDECG 1990; Lucas 1989).

Daily inhalation rates (in m^3/day and/or m^3/kg-day) are notably used to adjust data from human occupational and laboratory animal exposure assessments via inhalation of toxic compounds for the determination of some reference concentrations (RfCs) and many criteria/guideline values (e.g., in µg/m^3). The latter values as well as RfCs are regulating and restricting air pollutant concentrations in the environment (Benson *et al.* 2002; Health Canada 1996). These inhalation rates are also used to estimate intakes and uptakes (*e.g.*, in µg/m^3 and/or µg/kg-day) by individuals exposed to airborne chemical concentrations (Paustenbach 2001). Oxygen intake from daily air inhalation is consumed to fill physiological needs which vary according to the total daily energy requirements (TDERs) of the individual (IDECG 1990; Layton 1993; Lucas 1989). The main component of the TDER, the basal metabolic rate (BMR), is nearly proportional to body weight. Moreover, increments in energy expenditures brought about by most physical activities where body weight is supported against gravity (e.g. walking, but not cycling on a stationary cycle ergometer) are also directly proportional to body weight and constitute another portion of the TDER (IDECG 1990; IOM 2002; Lucas 1989). However, there has been no study to evaluate daily inhalation rates according to body weight for a single cohort of individuals. Daily inhalation estimates for a given population of individuals are simply associated with body weights from another population of the same age group (Finley *et al.* 1994; Layton 1993; Richardson 1997). Using such practices, underweight values overestimate daily inhalation rates whereas overweight values underestimate them, when daily inhalation estimates are expressed per unit of body weight (Torun *et al.* 1996). Therefore, it is essential to obtain daily inhalation estimates per unit of body weight that are close to biological reality in order to estimate daily intakes and uptakes resulting from air pollutant exposure and thus reach proper decision for regulatory purposes. Errors are also introduced in establishing criteria and guideline values when the distribution of breathing rates is considered independent of the distribution of body weights.

The doubly labeled water (DLW) method provides accurate and precise TDEE measurements for unrestrained free-living males and females from birth to old age during real-life situations in their normal surroundings (Butte 2000; IDECG 1990; IOM 2002; Lucas 1989). It also provides the most accurate measure of the energy cost for growth (ECG) for young individuals during the first years of life up to pubertal ages (Butte *et al.* 1990; Butte 2000; Butte *et al.* 2000). The DLW method measures the turnover of hydrogen and oxygen into water as well as the carbon dioxide rate production by monitoring the differential disappearance of the stable isotopes deuterium (^{2}H) and heavy oxygen-18 (^{18}O) in urine, saliva or blood samples by gas-isotope-ratio mass spectrometry of free-living people over a long period of time – from 7 to 21 days, after subjects have been given an oral loading dose of doubly labeled water: $^{2}H_2O$ and $H_2{}^{18}O$ (Butte 2000; Butte *et al.* 1990; IDECG 1990; IOM 2002; Lucas 1989; Torun *et al.* 1996). This method provides the most exact quantitative TDEE and ECG measurements for males and females. Those measurements can be converted into physiological daily inhalation rates using the equation developed by Layton (1993). The resulting inhalation rates can easily be expressed per unit of body weight because the DLW method requires systematic weight and body mass index (BMI) measurements of all subjects. BMRs are also measured by indirect calorimetry (Butte 2000; IDECG 1990; IOM 2002; Lucas 1989). The present paper is intended to determine physiological daily inhalation rates as a function of age for individuals aged 1 month to 96 years old based on DLW measurements. The first objective is to establish adequate daily inhalation rates for air quality and standard calculations for non-carcinogenic compounds. The second objective is to obtain distribution percentile values for males and females who inhale the highest volumes of air per kg of body weight (thus predisposed to larger intake of air pollutants by the respiratory tract) for use in health risk assessment.

RELEVANT METHODOLOGICAL APPROACHES

Study Design and Subjects

The present study was designed to calculate physiological daily inhalation rates (expressed in m^3/day and m^3/kg-day) for a wide range of individuals taken from different age groups and physiological conditions: healthy newborns aged 3 to 5 weeks old (n=33), healthy normal-weight males and females aged 2.6 months to 96 years (n=1252), low-BMI subjects (underweight women, n=17; adults from less affluent societies, n=59) and overweight/obese individuals (n=679) as well as athletes, explorers and soldiers when reaching very high energy expenditures (n=170). Data for underweight, healthy normal-weight and overweight/obese individuals were gathered and defined according to BMI cut-offs. Data for newborns were included regardless of BMI values, since they have been clinically evaluated as being healthy infants. Underweight adults are defined as those having BMIs lower than 18.5 kg/m^2. Healthy normal-weight individuals are defined as those having BMIs between the 3rd and 97th percentiles for infants and toddlers under 3 years old, corresponding to the 85th percentile or below for children and teenagers aged

3 to 19 years, and varying between 18.5 and 24.5 kg/m^2 for adults over 19 up to 96 years. Of course, overweight individuals are defined as those having BMIs higher than the 97th percentiles for infants and toddlers under 3 years old and higher than the 85th percentile for individuals aged 3 to 19 years. Overweight adults over 19 years of age have BMIs varying from 25 to 30 kg/m^2, whereas obese individuals have BMIs greater than 30 kg/m^2 (Kuczmarski *et al.* 2000; NHLBI/NIDDK 1998; Toriano *et al.* 1995; WHO 1998).

The aggregate data for normal-weight and overweight/obese males (n=746) and females (n=1185) were grouped in smaller age groups of 30 subjects. Means and standard deviations of body weights, BMIs, basal energy expenditures (BEEs), TDERs and daily metabolic equivalent values (DMET) or TDER/BEE ratios have been calculated for all sub-groups as well as for newborns. BEEs correspond to BMRs expressed on a 24-hour basis, whereas DMETs (daily BEE multiplier) represent physical activity levels or PAL when adding the ECG. Physiological daily inhalation rates have been calculated for each age group. For each set of data concerning overweight/obese age groups, additional set of values have been calculated based on normal-weight parameters for comparison purposes. Mean age statistical differences between each age group of normal-weight and overweight/obese individuals have been calculated by using Mann-Whitney tests. The 1st and 99th percentiles of the age for underweight sub-groups and athletes, explorer and soldiers have been derived from the standard deviations associated with their mean ages in order to estimate the ECG values. Distributions of the physiological daily inhalation rates and the associated statistical *p* values bases on the Shapiro-Wilk normality tests have been calculated for each normal-weight and overweight/obese sub-group.

Data Selection

Published mean measured data for formula-fed very low-birth-weight infants aged 3 weeks in Reichman *et al.* (1981, 1982) and breastfed and formula-fed infants aged 1 month in Butte *et al.* (1990) as well as data reported in Black *et al.* (1996) for underweight women with anorexia nervosa, adults from less affluent societies (low-BMI subjects), athletes, explorers and soldiers have been used in the present paper (n=279). A database reported in the IOM (2002) has been preferentially used to characterize normal-weight and overweight/obese groups because individual data including BMI, body weight, BMR and TDEE measurements were available for each of the 1931 subjects aged 2.6 months to 96 years. Such sets of measured values per subject, which were essentials for adequate data calculations per age and BMI sub-groups, were not available in other studies as in Black *et al.* (1996), Coward (1998) and Torun *et al.* (1996). TDEEs over a 6-hour period for infants aged 3 weeks, sleeping metabolic rates and minimal observable energy expenditures for 1-month old infants as well as BEEs for males and females aged 2.6 months to 96 years were measured by indirect calorimetry (Black *et al.* 1996; Butte *et al.* 1990; Reichman *et al.* 1981, 1982; IOM 2002). The nutritional balance for infants aged 3 weeks was determined by measurements of intakes (formula) and outputs (urine and stool) over three days (Reichman *et al.* 1981, 1982). TDEE measurements from the DLW method were based on the monitoring of stable isotopic forms of water ($^{2}H_2O$ and $H_2{}^{18}O$) in urine samples from unrestrained free-living males and females during real-life situations in their normal surroundings. Deuterium (^{2}H) and heavy oxygen-18 (^{18}O) were measured by gas-isotope-ratio mass spectrometry during 14-day periods in Butte *et al.* (1990) and for a duration varying between 7 to 21 days in other studies reported in Black *et al.* (1996) and IOM (2002), thus totalizing an aggregate period of over 30,000 days.

Doubly Labeled Water Method

The first field applications of the DLW method in human subjects based on the work of Lifson *et al.* (1955) were reported in Schoeller and van Santen (1982) and Prentice *et al.* (1985). This was made possible due to the increased sensitivity and accuracy of isotope measurements by gas-isotope-ratio mass spectrometers (IDECG 1990). Rapid expansion of the literature using the DLW method has been observed since then with a tremendous number of studies on TDEEs for small cohorts of free-living males and females. The disappearance rate of deuterium (^{2}H) with the DLW method reflects water output and that of heavy oxygen-18 (^{18}O) represents water output plus carbon dioxide (CO_2) production rates, because of the rapid equilibration of the body water and bicarbonate pools by carbonic anhydrase. Differences between the two disappearance rates are therefore used to calculate the CO_2 production rate. The energy released per liter of CO_2 varies with the average respiratory quotient and hence with the substrate mixture oxidized by the body. TDEEs are determined from CO_2 production rates using classic respirometry formulas in which values for the respiratory quotient ($RQ = CO_{2\ produced} / O_{2\ consumed}$) are derived from the composition of the diet during the period of time of each study. The ratio of the CO_2 produced versus the O_2 consumed by the biological oxidation of a representative sample of the diet (RQ) can also be measured directly by respiratory gas exchange measurements. Nevertheless, the respiratory quotient has a relatively small effect on DLW measurements of TDEEs. The precision of DLW measurements, as assessed by the variability of the individual's DLW measurements from indirect calorimetry assessments, varies between 2 to 5% in different validation studies (IDECG 1990; Torun *et al.* 1996).

Physiological Daily Inhalation Calculations

TDEE measurements encompass all daily energy expenditures of free-living people, except for the ECG which is determined in the present paper from DLW measurements (Butte 2000; Butte *et al.* 1990, 2000; IDECG 1990; Lucas 1989). Summation of the TDEE and ECG constitutes the TDER value, which in turn is converted in the present paper into physiological daily inhalation rates, using the Layton equation:

$$PDIR = (TDEE + ECG) * H * VQ * 10^{-3} \quad \text{Equation 1}$$

Where,

PDIR = physiological daily inhalation rate (m^3/day)

TDEE = total daily energy expenditure (kcal/day)

ECG = stored daily energy cost for growth (kcal/day)

H = oxygen uptake factor, volume of 0.21 L of oxygen (at standard temperature and pressure, dry air) consumed to produce 1 kcal of energy expended

VQ = ventilatory equivalent ratio of the minute volume (V_E at body temperature pressure saturation) to the oxygen uptake rate (VO_2 at standard temperature and pressure, dry air) $V_E/VO_2 = 27$ (unitless)

10^{-3} = conversion factor (L/m^3)

Metabolic oxidation of each gram of carbohydrate, protein and fat requires the metabolic consumption of 0.83, 0.97 and 2 liters of oxygen (O_2) respectively and yields energy production rates of 5.0, 4.5 and 4.7 kcal/L of O_2 respectively (Layton 1993). An H value of 0.21 L O_2 $kcal^{-1}$ has been calculated by Layton (1993), based on the mean nutriment intake contributions of an American population (16% of protein, 39.8% of fat, and 43.6% of carbohydrate). Using Canadian mean nutriment intake contributions observed and compiled by Brault-Dubuc and Mongeau (1989) during a 10-year span (14.2% of protein, 37.7% of fat, 48.6% of carbohydrate), a comparable weighted average breakdown of an H value was calculated. Thus, the H value of 0.21 L O_2 $kcal^{-1}$was used in the present paper.

Energy Cost for Growth

The ECG must be added to the TDEE to obtain the TDER values (Butte 2000; Lucas 1989). The ECG varies during childhood, particularly during the childhood adiposity rebound and adolescent growth spurt. ECG values as a function of age have been calculated from DLW measurements in regard to 933 infants, children and adolescents by Butte (2000) and Butte *et al.* (1990, 2000), in consistency with Tanner's weight velocities and the energy content of 20 kJ/g tissue deposits (Tanner *et al.* 1996).

Growth in the first two years of life

Growth during the first two years of life is characterized by a gradual deceleration in both linear growth velocity and weight gain rates, both of which level off at 2 to 3 years of age (Rogol *et al.* 2000). During this period, infants exhibit the pattern of growth that is consistent with their genetic backgrounds. Physiological measurements performed in 13 infants aged 3 weeks demonstrated that the ECG corresponds to a mean increase of 108% of the TDEE (Reichman *et al.* 1981, 1982). The ECG for 10 breastfed infants aged 1 month (+45% of the TDEE) based on DLW measurements has been shown by Butte *et al.* (1990) to be lower than the ECG for 10 formula-fed infants of the same age (+63% of the TDEE). ECGs for breastfed and formula-fed girls and boys aged 1 month or less require mean increases of 43.6 and 46.3% of the TDEE respectively (Table Web-1; Butte

2000). Increases of 58 and 63% of the TDEE are required for ECGs for girls and boys respectively aged between 1 and 2 months. The ECG then drops dramatically with age and reaches lowest values of 1.5 and 1.7% of the TDEE at 2 years of age for boys and girls respectively (Butte *et al.* 1990, n=40; Butte 2000, n=338; Butte *et al.* 2000, n=67).

Prepubertal growth

Prepubertal growth is a relatively stable process. Infancy shifts in the growth pattern are complete and the child follows the trajectory attained previously. The lowest values for growth velocity reached at the age of 2 years maintain the same level between 3 to less than 5 years of age (+1.5% of the TDEE for boys; +1.7% of the TDEE for girls; n=192 for both genders). The ECG remains low until the pubertal growth spurt with a TDEE increase similar to the increase in children aged 1 year (Butte 2000; Butte *et al.* 2000; IOM 2002; n=556). The ECG for girls aged 5 to less than 11 years corresponds to a TDEE increase of 2.5%, compared to 3.0% for boys aged 5 to less than 13 years.

Pubertal growth

Puberty is a dynamic period of development marked by rapid changes in body size, shape and composition, all of which are sexually dimorphic (Rogol *et al.* 2000). Puberty in girls begins approximately at the age of 9 or 10 years and usually culminates with the onset of menstruation between ages of 11 and 16 years, while puberty in boys begins at 13 years (Guyton 1991). The onset of puberty also corresponds to a skeletal (biological) age of approximately 11 years for girls and 13 for boys (Rogol *et al.* 2000; Tanner *et al.* 1975). Complete process of pubertal growth spurts for teenagers and young adults is carried out between 11 and 18 years old for females and between 13 and 20 years for males, but may also continue for the latter until 25 years of age: deposition of bone minerals, fat free and fat mass accumulations, increases in skeletal size and in muscle mass, gain in stature, lean body mass and body weight, and epiphyseal fusion (Forbes 1987; Rogol *et al.* 2000; IOM 2002). Based on DLW measurements (n=93), the ECG for teenagers and young adults requires an increase of 4.2% of the TDEE in females aged 11 to 18 years and males aged 13 to 20 years (Table Web-1; Butte 2000; Forbes 1987; IOM 2002). The ECG for males decreases between 4.2 to 0.0% according to age from 20 up to 25 years (Table Web-1; Butte 2000; Forbes 1987; IOM 2002). Thus, proportional decrease values of ECG for males are considered in the present paper, namely calculated as being 3.3, 2.5, 1.7 and 0.8% of the TDEE for males aged 21, 22, 23 and 24 years respectively (Table Web-1).

RESULTS AND STATISTICAL ANALYSIS

Tables Web-1 to Web-12 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web Site (MDDEP 2006) and may be consulted in English at: http://www.mddep.gouv.qc.ca/air/inhalation/index-en.htm, or in French at: http://www.mddep.gouv.qc.ca/air/inhalation/index.htm. Further information can also be obtained by contacting the authors. Tables 13 to 22 are part of the present paper. ECGs for males and females from birth up to 25 years of age (in % of TDEE) are given in Table Web-1. Means of measured body weights (in kg) with standard deviation (S.D.) values are reported in Tables Web-2, Web-3, Web-5, Web-7, and Web-10 to Web-12 and in Tables 13, 14, 16, 17 and 20 to 22. BMI measurements (means in kg/m^2 ± S.D.) are presented in Tables Web-4, Web-6, Web-8, and Web-10 to Web-12. BEEs measured by indirect calorimetry and TDEEs from DLW measurements (means in kcal/day and kcal/kg-day ± S.D.) are reported in Tables Web-2, Web-3, Web-5, Web-7 and Web-10 to Web 12. ECGs and TDERs (means in kcal/day and kcal/kg-day ± S.D.) for newborns, normal-weight, overweight/obese and underweight individuals as well as adults from less affluent societies are summarized in Tables Web-2, Web-4, Web-6, Web-8, Web-10 and Web-11. Similar mean data for athletes, explorers and soldiers are presented in Table Web-12. Mean physiological daily inhalation rates for newborns (in m^3/day and m^3/kg-day ± S.D.) are presented in Table 13. Those data are consistent with values related to older infants (Tables 14 to 19). No distribution is however given for newborns since the normality hypothesis could not be tested due to the insufficient number of observations for each sub-population (10 to 13). Distribution of physiological daily inhalation rates and observed p values for normal-weight and overweight/obese sub-groups of individuals are given in Tables 14, 16 and 17 for percentile values expressed in m^3/day, and in Tables 15, 18 and 19 for values expressed in m^3/kg-day. In Tables 20 to 22, mean physiological daily inhalation rates (in m^3/day and m^3/kg-day ± S.D.) for underweight women, adults from less affluent societies, athletes, explorers and soldiers are also given. DMET values (± S.D.) are reported for each sub-group of individuals in Tables 13, 15 and 18 to 22.

Results of Mann-Whitney statistical tests are presented in Table Web-9. Mean ages of 7 out of 12 sets of normal-weight and overweight/obese sub-groups are statistically different ($p < 0.05$). However, such differences are small compared the wide span of age in most age groups. For instance, mean ages between each sub-group of females aged more than 5 to 9 years are different by 3 months, while those for sub-groups aged more than 9 to 18 years old are different by 1.5 years (Table Web-9). Moreover, physiological daily inhalation rates expressed in m^3/kg-day for most sub-populations in normal-weight and overweight/obese groups determined for individuals aged 2.6 months to 96 years

(Tables 15, 18 and 19) are consistent with normality distributions based on Shapiro-Wilk normality tests ($p \geq 0.05$). Percentile physiological daily inhalation rates for the few other sub-populations in normal-weight groups ($p < 0.05$), calculated under the normality hypothesis, have been considered as being conservative for use in air quality criteria and guideline calculations. Moreover, physiological daily inhalation values for 91% of sub-populations in normal-weight groups are equal to or higher than a p value of 0.01 (Table 15). Positive skewness values and kurtosis values higher than 3 have been calculated in all cases, except for one age group (girls aged 1 to 2 years) whose kurtosis value is 1.73. Finally, means, standard deviations and percentile physiological daily inhalation rates for all sub-populations in normal and overweight/obese groups as well as comparison between female and male values were in all cases biologically consistent. Thus, assuming normality for all sub-populations or age groups was statistically justified (Tables 14 to 19).

DISCUSSION

TDERs and physiological daily inhalation rates clearly show a decrease as a function of age from birth to adulthood (Tables Web-2 and Web-4). When children from normal-weight groups reach 11 years of age, the TDER sharply drops by 12.7 kcal/kg-day for boys and 14.6 kcal/kg-day for girls (-19.4% and -23.6% respectively). This is a clear deceleration compared to the decrease rate in younger children (Table Web-4). Similarly sharp TDER decelerations are shown in overweight/obese groups dropping by 14.2 kcal/kg-day for boys and 12.3 kcal/kg-day for girls once they exceeded 9 years of age (Tables Web-6 and Web-8). Such pattern is consistent with the remarkable increase in alveoli number and pulmonary gas-exchange surfaces from birth to about 8 years old, which ensures higher CO_2 and O_2 exchanges per unit of body weight for lower minute ventilation; the number of alveoli still increases very slowly beyond 8 years of age, whereas the size of alveolar structures grows linearly throughout early adolescence (Polgar and Weng 1979).

Physiological daily inhalation rates in m^3/kg-day drop by about 66 to 76% within the course of a lifetime (Tables 13 and 15). Rates for normal-weight and overweight/obese children aged 4 to 5 years (n=269) are between 1.5 and 2.7 times higher than values for normal active adults aged 18 to 96 years (Tables 18 and 19; n=768). Nevertheless, as measured by Prentice *et al.* (1996) with adult subjects (n=319) using the DLW method, despite the fact that overweight/obese individuals (n=679) are inhaling between 0.8 to 3.0 m^3 more air per day than normal-weight individuals (Tables 16 and 17), their physiological daily inhalation rates are 6 to 21% lower than that of their leaner counterparts (n=930) when expressed in m^3/kg-day (Tables 18 and 19). Consequently, healthy newborns aged 3 to 5 weeks and normal-weight infants aged 2.6 months to less than 6 months (n=118) inhale more air per unit of body weight (0.504 to 0.739 m^3/kg-day) than any overweight/obese or older normal-weight individual with normal active life styles (n=1846). Their physiological daily inhalation rates (Tables 13 and 15) are also higher than those for underweight adult females with anorexia nervosa (Table 21; 0.244 to 0.382 m^3/kg-day n=17) and also greater than 87% of those for athletes, explorers, soldiers and adults from less affluent societies (Tables 20 and 22; 0.181 to 0.456 m^3/kg-day, n=187). As underlined by Black *et al.* (1996), daily inhalation rates for other (13%) extremely active individuals during short term periods (0.512 to 0.672 m^3/kg-day, n=33) are expected to be lower when based on a basis of whole-year average, considering that such physical requirements (DMET > 4) are not sustainable as a permanent way of life.

Physiological daily inhalation rates for newborns and normal-weight infants aged 2.6 to less than 6 months are 2.1 to 5.1 times higher than those of normal-weight and overweight/obese adults aged 18 to 96 years with normal active life styles (Tables 13, 15, 18 and 19). These inhalation rates are also higher than the highest mean values that have been calculated by Brochu *et al.* (2006b) for pregnant and lactating teenage girls and women aged 11 to 55 years (n=357), based on DLW measurements (0.385 ± 0.110 and 0.383 ± 0.064 m^3/kg-day respectively). The 99th percentile physiological daily inhalation rates of 0.721 and 0.725 m^3/kg-day for normal-weight girls and boys aged 2.6 to less than 6 months respectively are higher than the highest percentile of 0.622 m^3/kg-day in gravid females and 0.647 m^3/kg-day in breastfeeding females that have been determined in Brochu *et al.* (2006b). The high daily inhalation values for newborns are consistent with their DMETs (Table 13). Mean values of 1.89 and 2.11 for newborns aged 1 month are as high as those for some female athletes (mountaineers, swimmers, runners during training) and male soldiers during base camp and field training (Tables 13 and 22). However, newborns aged 3 weeks show a higher mean DMET value reaching 2.77, which is as high as those for most male and female athletes (mountaineers, swimmers, cross-country skiers, runners during training, endurance runners) and male soldiers during almost all types of demanding training including jungle, winter and Arctic training (Tables 13 and 22).

Over the last 20 years, the results of factorial and physiological studies on 24-hour daily inhalation rates have raised the question of adequate values for the determination of air quality criteria and the setting of standard values. For example, Health Canada (1996) uses a daily inhalation rate of 0.444 m^3/kg-day to calculate the tolerable daily intake by inhalation of non-carcinogenic chemicals (i.e. 12 m^3/day for 27 kg, for children aged 5 to 11 years). This compares to the daily inhalation estimate of 0.286 m^3/kg-day, which has been published by the Federal Register in 1980 and is still used by many scientists (i.e. 20 m^3/day for a 70-kg adult). Health Canada (1996) was first to calculate the tolerable daily intake for non-carcinogenic compounds using inhalation rates for children. However, based on the present physiological values, the rate of 0.444 m^3/kg-day is adequate for boys aged 2 to less than 5 years but not for children 5 to 11 years of age (Table 15). On the other hand, newborns aged 3 weeks to 1 month as well as more than 75% of children aged 2.6 months to less than 11 years inhale more toxic chemicals than associated safe doses which are not anticipated to result in any adverse effects in humans, when air concentration reaches the air quality criteria and standard values determined by using the rate of 0.286 m^3/kg-day from the Federal Register (Tables 13 and 15). Moreover, the upper 99^{th} percentile value of 0.725 m^3/kg-day in Table 15 would be more appropriate as a default value than the rate of 0.59 m^3/kg-day (single value of Layton for infants aged less than 1 year) selected by the Department of Pesticide Regulation in California to represent all children in health risk assessment when duration of activity and activity pattern are not specified (USEPA 2000).

Among the numerous physiological daily inhalation rates given in the present paper, only a few will have an important health risk assessment utility for Canadian and American populations. For instance, only 2% of Canadian adults were underweight in 1996-1997

(Gilmore 1999). In addition, athletes and explorers constitute an exceptional small sample of the population. However, Canadian and American populations include a large percentage of overweight/obese individuals. For example, 46% of Canadian adults in 1996-1997 and 65% of their American counterparts in 1999-2000 were overweight or obese (Gilmore 1999; NCHS 2003; Willms *et al.* 2003). Considering the fact that healthy normal-weight individuals inhale larger volumes of air per kg of weight than their overweight/obese counterparts, daily inhalation values expressed in m^3/kg-day for the former will provide adequate protection in health risk assessment for the latter. However, inhalation data given in the present paper compared with those in Brochu *et al.* (2006b) yield to the conclusion that physiological daily inhalation rates for under-, normal- and overweight/obese pregnant and lactating females in m^3/day and m^3/kg-day are higher than those for males. For instance, in normal-weight subjects, females are susceptible to higher intakes of air pollutants by the respiratory tract than males by 18 to 41% throughout pregnancy and 23 to 39% during postpartum weeks. Therefore, the distribution of physiological daily inhalation rates presented in Brochu *et al.* (2006b) is recommended for health risk assessment for gravid and breast-feeding females. Finally, considering that males inhale more air per unit of body weight than non-gravid and non-lactating females, the distribution of physiological daily inhalation rates given in the present paper for healthy normal-weight males are appropriate for use in health risk assessment ($p \geq 0.03$) to ensure the protection of all individuals other than pregnant and lactating females for both the Canadian and American populations.

CONCLUSION

We recommend that the 99th percentile physiological daily inhalation rate of 0.725 m^3/kg-day for normal-weight boys aged 2.6 to less than 6 months be set for air quality criteria and standard calculations for non-carcinogenic compounds ($p \geq 0.05$ based on the Shapiro-Wilk normality test). This will ensure that less than 1% of infants aged 2.6 to less than 6 months and of course no older individual up to 96 years old with normal active life styles (including pregnant and lactating females as well as overweight/obese individuals) inhale more toxic chemicals than associated previously mentioned safe doses, when air concentration reaches the resulting air quality criteria and standard values. Using this physiological rate, criteria and standard values might be protective for most newborns aged 1 month and younger, considering their mean physiological daily inhalation rates.

Newborns are less exposed to outdoor environmental air contaminants than older individuals. Nevertheless, because they have smaller pseudoalveolar structures, hence smaller gas exchange pulmonary surfaces, newborns do breathe larger volumes of air than older individuals to be sufficiently oxygenated. Thus, a temporary slightly higher physiological daily inhalation rate of 0.956 m^3/kg-day is recommended for short-term criteria and standard calculations for toxic chemicals that yield adverse effects over short exposure periods (instantaneous to short-term duration). The latter rate corresponds to the estimated 99th percentile of the physiological daily inhalation rate based on the mean TDER and physiological daily inhalation values for newborns aged 21 days, assuming normality (130.4 ± 16.4 kcal/kg-day and 0.739 ± 0.093 m^3/kg-day respectively). This rate is recommended temporarily, until more TDER values are measured with the DLW method and for a larger number of newborn subjects. Future studies on physiological daily inhalation rates for individuals with pre-existing medical conditions rendering a greater susceptibility to toxicants are however recommended since this aspect has not been covered in the present paper.

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Table 13 Physiological daily inhalation rates for newborns aged 1 month or less

Age group (days)	*n*	Body weight (kg)	Physiological daily inhalation rate[e] Mean ± S.D.		DMET[h] *(unitless)*
		Mean ± S.D.	(m^3/day)	(m^3/kg-day)	Mean ± S.D.
21 (3 weeks)	13[a, c]	1.2 ± 0.2	0.85 ± 0.17[f]	0.739 ± 0.093[f]	2.77 ± 0.41
32 (~ 1 month)	10[b, d]	4.7 ± 0.7	2.45 ± 0.59[g]	0.527 ± 0.096[g]	1.89 ± 0.38
33 (~ 1 month)	10[a, d]	4.8 ± 0.3	2.99 ± 0.47[g]	0.618 ± 0.090[g]	2.11 ± 0.36

[a]Formula-fed infants. [b]Breastfed infants. [c]Healthy infants with very low birth weight (Reichman *et al.* 1981, 1982).

[d]Infants evaluated as being clinically healthy and neither underweight nor overweight (Butte *et al.* 1990).

[e]Total daily energy requirements (TDERs) reported in Table Web-2 were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and $V_E/VO_2 = 27$ (Layton 1993). TDER = total daily energy requirement. TDER = (TDEE + ECG). TDEE = total daily energy expenditure. ECG = stored daily energy cost for growth. ECGs from Table Web-1 were initially added to the basic TDEEs in order to obtain the appropriate TDERs (Table Web-2).

[f]TDEEs based on nutritional balance measurements (intake and output analysis) during 3-day periods for each infant.

[g]TDEEs based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 14-day periods.

[h]Daily metabolic equivalent or daily BEE multiplier (TDER/BEE). BEEs or basal energy expenditures (BMRs expressed on a 24-hour basis) were measured by indirect calorimetry (Butte *et al.* 1990; Reichman *et al.* 1981, 1982).

Tables Web-1 and Web-2 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006). *n*= number of individuals; S.D. = standard deviation.

Table 14 Distribution percentiles of physiological daily inhalation rates (m^3/day) for free-living normal-weight males and females aged 2.6 months to 96 years

Gender and age group (years)	*n*	Body weight[a] (kg) Mean ± S.D.	*Observed p value*[b]	Physiological daily inhalation rates[c] (m^3/day): Mean ± S.D.	Percentile[d]: 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
Males														
0.22 to < 0.5	32	6.7 ± 1.0	0.032	3.38 ± 0.72	1.97	2.19	2.46	2.89	3.38	3.87	4.30	4.57	4.79	5.06
0.5 to < 1	40	8.8 ± 1.1	0.700	4.22 ± 0.79	2.68	2.92	3.21	3.69	4.22	4.75	5.23	5.51	5.76	6.05
1 to < 2	35	10.6 ± 1.1	0.898	5.12 ± 0.88	3.40	3.68	3.99	4.53	5.12	5.71	6.25	6.56	6.84	7.16
2 to < 5	25	15.3 ± 3.4	0.101	7.60 ± 1.28	5.08	5.49	5.95	6.73	7.60	8.47	9.25	9.71	10.12	10.59
5 to < 7	96	19.8 ± 2.1	0.176	8.64 ± 1.23	6.23	6.61	7.06	7.81	8.64	9.47	10.21	10.66	11.05	11.50
7 to < 11	38	28.9 ± 5.6	0.326	10.59 ± 1.99	6.69	7.32	8.04	9.25	10.59	11.94	13.14	13.87	14.49	15.22
11 to < 23	30	58.6 ± 13.9	0.851	17.23 ± 3.67	10.04	11.19	12.53	14.75	17.23	19.70	21.93	23.26	24.41	25.76
23 to < 30	34	70.9 ± 6.5	0.238	17.48 ± 2.81	11.97	12.86	13.88	15.59	17.48	19.38	21.08	22.11	22.99	24.02
30 to < 40	41	71.5 ± 6.8	0.087	16.88 ± 2.50	11.98	12.77	13.68	15.20	16.88	18.57	20.09	21.00	21.79	22.70
40 to < 65	33	71.1 ± 7.2	0.275	16.24 ± 2.67	11.00	11.84	12.81	14.44	16.24	18.04	19.67	20.64	21.48	22.46
65 to ≤ 96	50	68.9 ± 6.7	0.293	12.96 ± 2.48	8.11	8.89	9.79	11.29	12.96	14.63	16.13	17.03	17.81	18.72
Females														
0.22 to < 0.5	53	6.5 ± 0.9	0.002	3.26 ± 0.66	1.96	2.17	2.41	2.81	3.26	3.71	4.11	4.36	4.56	4.81
0.5 to < 1	63	8.5 ± 1.0	0.699	3.96 ± 0.72	2.56	2.78	3.05	3.48	3.96	4.45	4.88	5.14	5.37	5.63
1 to < 2	66	10.6 ± 1.3	0.044	4.78 ± 0.96	2.90	3.20	3.55	4.13	4.78	5.43	6.01	6.36	6.67	7.02
2 to < 5	36	14.4 ± 3.0	0.114	7.06 ± 1.16	4.79	5.15	5.57	6.28	7.06	7.84	8.54	8.97	9.33	9.76
5 to < 7	102	19.7 ± 2.3	0.699	8.22 ± 1.31	5.65	6.06	6.54	7.34	8.22	9.11	9.90	10.38	10.79	11.27
7 to < 11	161	28.3 ± 4.4	0.0001	9.84 ± 1.69	6.53	7.07	7.68	8.70	9.84	10.98	12.00	12.61	13.15	13.76
11 to < 23	87	50.0 ± 8.9	0.895	13.28 ± 2.60	8.18	9.00	9.94	11.52	13.28	15.03	16.61	17.56	18.38	19.33
23 to < 30	68	59.2 ± 6.6	0.266	13.67 ± 2.28	9.20	9.91	10.74	12.13	13.67	15.21	16.59	17.42	18.14	18.98
30 to < 40	59	58.7 ± 5.9	0.113	13.68 ± 1.76	10.22	10.78	11.42	12.49	13.68	14.87	15.94	16.58	17.13	17.78
40 to < 65	58	58.8 ± 5.1	0.561	12.31 ± 2.07	8.26	8.91	9.66	10.92	12.31	13.70	14.96	15.71	16.36	17.12
65 to ≤ 96	45	57.2 ± 7.3	0.266	9.80 ± 2.17	5.55	6.24	7.02	8.34	9.80	11.27	12.58	13.37	14.06	14.85

[a]Measured body weight. Normal-weight individuals defined according to the body mass index (BMI) cut-offs. BMIs for sub-groups are reported in Table Web-4.

[b]Observed *p* values based on Shapiro-Wilk normality tests. Daily metabolic equivalent values are given in Table 15.

[c]Total daily energy requirements (TDERs) reported in Table Web-4 (in kcal/day) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG). TDEE = total daily energy expenditure. ECG = stored daily energy cost for growth. TDEEs in Table Web-3 were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for 1252 individuals aged 2.6 months to 96 years (IOM 2002). ECGs from Table Web-1 were initially added to the basic TDEEs in order to obtain the appropriate TDERs.

[d]Percentiles based on a normal distribution assumption for all age groups. *n* =number of individuals; S.D.=standard deviation.

Tables Web-1, Web-3 and Web-4 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 15 Distribution percentiles of physiological daily inhalation rates per unit of body weight (m^3/kg-day) for free-living normal-weight males and females aged 2.6 months to 96 years

Gender and age group (years)	Observed *p* value [a]	Physiological daily inhalation rates [b] (m^3/kg-day) Mean ± S.D.	Percentile [c] 2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th	DMET [d] (unitless) Mean ± S.D.
Males													
0.22 to < 0.5	0.823	0.509 ± 0.093	0.327	0.356	0.390	0.447	0.509	0.571	0.627	0.661	0.690	0.725	1.55 ± 0.28
0.5 to < 1	0.302	0.479 ± 0.071	0.341	0.363	0.389	0.432	0.479	0.526	0.570	0.595	0.618	0.644	1.40 ± 0.22
1 to < 2	0.706	0.480 ± 0.059	0.364	0.383	0.405	0.441	0.480	0.520	0.556	0.578	0.596	0.618	1.36 ± 0.22
2 to < 5	0.304	0.444 ± 0.042	0.362	0.375	0.391	0.416	0.444	0.472	0.497	0.512	0.526	0.541	1.41 ± 0.16
5 to < 7	0.037	0.415 ± 0.047	0.322	0.337	0.354	0.383	0.415	0.446	0.475	0.492	0.507	0.524	1.42 ± 0.15
7 to < 11	0.525	0.372 ± 0.062	0.251	0.270	0.293	0.330	0.372	0.413	0.451	0.474	0.493	0.516	1.60 ± 0.23
11 to < 23	0.986	0.300 ± 0.047	0.207	0.222	0.239	0.268	0.300	0.331	0.360	0.377	0.392	0.410	1.82 ± 0.22
23 to < 30	0.348	0.247 ± 0.039	0.171	0.183	0.198	0.221	0.247	0.273	0.297	0.311	0.323	0.338	1.74 ± 0.24
30 to < 40	0.030	0.237 ± 0.034	0.170	0.181	0.193	0.214	0.237	0.260	0.281	0.293	0.304	0.317	1.78 ± 0.21
40 to < 65	0.649	0.230 ± 0.042	0.148	0.161	0.176	0.202	0.230	0.258	0.284	0.299	0.313	0.328	1.76 ± 0.27
65 to ≤ 96	0.967	0.188 ± 0.031	0.128	0.137	0.149	0.168	0.188	0.209	0.228	0.239	0.249	0.260	1.55 ± 0.25
Females													
0.22 to < 0.5	0.011	0.504 ± 0.093	0.322	0.351	0.385	0.442	0.504	0.566	0.623	0.657	0.686	0.721	1.56 ± 0.29
0.5 to < 1	0.371	0.463 ± 0.064	0.338	0.358	0.382	0.421	0.463	0.506	0.545	0.568	0.588	0.612	1.39 ± 0.21
1 to < 2	0.007	0.451 ± 0.077	0.301	0.325	0.353	0.399	0.451	0.502	0.549	0.577	0.601	0.630	1.34 ± 0.25
2 to < 5	0.274	0.441 ± 0.071	0.301	0.323	0.350	0.393	0.441	0.489	0.532	0.559	0.581	0.607	1.44 ± 0.26
5 to < 7	0.037	0.395 ± 0.048	0.300	0.315	0.333	0.362	0.395	0.427	0.457	0.474	0.489	0.507	1.45 ± 0.18
7 to < 11	0.148	0.352 ± 0.062	0.231	0.251	0.273	0.311	0.352	0.393	0.431	0.453	0.473	0.496	1.59 ± 0.24
11 to < 23	0.190	0.269 ± 0.049	0.173	0.189	0.207	0.236	0.269	0.302	0.331	0.349	0.365	0.383	1.78 ± 0.29
23 to < 30	0.004	0.233 ± 0.042	0.150	0.163	0.179	0.204	0.233	0.261	0.287	0.302	0.315	0.331	1.79 ± 0.29
30 to < 40	0.395	0.235 ± 0.035	0.167	0.178	0.191	0.212	0.235	0.258	0.279	0.292	0.303	0.316	1.83 ± 0.26
40 to < 65	0.482	0.211 ± 0.036	0.140	0.151	0.164	0.186	0.211	0.235	0.257	0.270	0.281	0.295	1.78 ± 0.27
65 to ≤ 96	0.010	0.172 ± 0.037	0.100	0.112	0.125	0.148	0.172	0.197	0.220	0.233	0.245	0.258	1.43 ± 0.30

[a] Observed *p* values based on Shapiro-Wilk normality tests. The number of individuals and measured body weights were gathered according to body mass index cut-offs and are given in Table 14. [b] Total daily energy requirements (TDERs) reported in Table Web-4 (in kcal/kg-day) were converted into physiological daily inhalation rates by the following equation: TDER*H*(V_E/VO_2)*10^{-3}. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG). TDEE = total daily energy expenditure. ECG = stored daily energy cost for growth. TDEEs in Table Web-3 were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for 1252 individuals aged 2.6 months to 96 years (IOM 2002). ECGs from Table Web-1 were initially added to the basic TDEEs in order to obtain the appropriate TDERs.
[c] Percentiles based on a normal distribution assumption for all age groups. [d] Daily metabolic equivalent or daily BEE multiplier (TDER/BEE). BEEs or basal energy expenditures (BMRs expressed on a 24-hour basis) were measured by indirect calorimetry (Table Web-3; IOM 2002).
Tables Web-1, Web-3 and Web-4 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 16 Distribution percentiles of physiological daily inhalation rates (m^3/day) for free-living normal-weight and overweight/obese males aged 4 to 96 years

Male age group (years)	*n*	Body weight[a] (kg) Mean ± S.D.	*Observed p value*[b]	Physiological daily inhalation rates[c] (m^3/day) Mean ± S.D.	Percentile[d] 2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
Normal-weight														
4 to < 5.1	77	19.0 ± 1.9	0.387	7.90 ± 0.97	6.00	6.31	6.66	7.25	7.90	8.56	9.15	9.50	9.81	10.16
5.1 to < 9.1	52	22.6 ± 3.5	0.157	9.14 ± 1.44	6.31	6.77	7.29	8.17	9.14	10.11	10.99	11.51	11.97	12.49
9.1 to <18.1	36	41.4 ± 12.1	0.307	13.69 ± 3.95	5.95	7.19	8.63	11.02	13.69	16.35	18.75	20.19	21.43	22.88
18.1 to < 40.1	98	71.3 ± 6.1	0.234	17.41 ± 2.70	12.11	12.96	13.94	15.58	17.41	19.23	20.87	21.85	22.70	23.69
40.1 to < 70.1	34	70.0 ± 7.8	0.374	15.60 ± 2.89	9.94	10.85	11.89	13.65	15.60	17.54	19.30	20.34	21.25	22.31
70.1 to ≤ 96	38	68.9 ± 6.8	0.655	12.69 ± 2.33	8.11	8.85	9.70	11.11	12.69	14.26	15.68	16.53	17.26	18.12
Overweight/obese														
4 to < 5.1	54	26.5 ± 4.9	0.454	9.59 ± 1.26	7.13	7.52	7.98	8.74	9.59	10.44	11.21	11.66	12.06	12.52
5.1 to < 9.1	40	32.5 ± 9.2	0.135	10.88 ± 2.49	6.00	6.78	7.69	9.20	10.88	12.56	14.07	14.98	15.77	16.68
9.1 to <18.1	33	55.8 ± 10.8	0.454	14.52 ± 1.98	10.63	11.25	11.98	13.18	14.52	15.85	17.06	17.78	18.40	19.13
18.1 to < 40.1	52	98.1 ± 25.2	0.245	20.39 ± 3.62	13.30	14.44	15.75	17.95	20.39	22.83	25.03	26.35	27.49	28.81
40.1 to < 70.1	81	93.2 ± 14.9	0.003	17.96 ± 3.71	10.68	11.85	13.20	15.45	17.96	20.46	22.71	24.06	25.23	26.59
70.1 to ≤ 96	32	82.3 ± 10.3	0.025	14.23 ± 2.94	8.47	9.40	10.46	12.25	14.23	16.21	18.00	19.06	19.99	21.07

[a]Measured body weight. Normal-weight and overweight/obese males defined according to the body mass index (BMI) cut-offs. BMIs for sub-groups are reported in Table Web-6.

[b]Observed *p* values based on Shapiro-Wilk normality tests. Daily metabolic equivalent values are given in Table 18.

[c]Total daily energy requirements (TDERs) reported in Table Web-6 (in kcal/day) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG). TDEE = total daily energy expenditure (Table Web-5). ECG = stored daily energy cost for growth (Table Web-6). TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for 627 males aged 4 to 96 years (IOM 2002). ECGs from Table Web-1 were initially added to the basic TDEEs in order to obtain the TDER values.

[d]Percentiles based on a normal distribution assumption for all age groups. *n* =number of individuals; S.D.=standard deviation.

Tables Web-1, Web-5 and Web-6 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 17 Distribution percentiles of physiological daily inhalation rates (m^3/day) for free-living normal-weight and overweight/obese females aged 4 to 96 years

Female age group (years)	*n*	Body weight[a] (kg) Mean ± S.D.	*Observed p value*[b]	Physiological daily inhalation rates[c] (m^3/day) Mean ± S.D.	Percentile[d] 2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
Normal-weight														
4 to < 5.1	82	18.7 ± 2.0	0.433	7.41 ± 0.91	5.63	5.92	6.25	6.80	7.41	8.02	8.57	8.90	9.19	9.52
5.1 to < 9.1	151	25.5 ± 4.1	0.036	9.39 ± 1.62	6.21	6.72	7.31	8.30	9.39	10.48	11.47	12.05	12.56	13.16
9.1 to <18.1	124	42.7 ± 11.1	0.005	12.04 ± 2.86	6.44	7.34	8.38	10.11	12.04	13.97	15.70	16.74	17.64	18.68
18.1 to < 40.1	135	59.1 ± 6.3	0.092	13.73 ± 2.01	9.78	10.41	11.15	12.37	13.73	15.09	16.31	17.04	17.68	18.41
40.1 to < 70.1	79	59.1 ± 5.3	0.450	11.93 ± 2.16	7.70	8.38	9.16	10.47	11.93	13.38	14.69	15.48	16.16	16.95
70.1 to ≤ 96	24	54.8 ± 7.5	0.430	8.87 ± 1.79	5.36	5.92	6.57	7.66	8.87	10.07	11.16	11.81	12.38	13.03
Overweight/obese														
4 to < 5.1	56	26.1 ± 5.5	0.771	8.70 ± 1.13	6.49	6.84	7.26	7.94	8.70	9.47	10.15	10.56	10.92	11.33
5.1 to < 9.1	68	34.6 ± 9.9	0.144	10.55 ± 2.23	6.18	6.88	7.69	9.05	10.55	12.06	13.41	14.22	14.93	15.75
9.1 to <18.1	68	59.2 ± 12.8	0.580	14.27 ± 2.70	8.98	9.83	10.81	12.45	14.27	16.09	17.73	18.71	19.56	20.55
18.1 to < 40.1	76	84.4 ± 16.3	0.285	15.66 ± 2.11	11.52	12.18	12.95	14.23	15.66	17.08	18.36	19.13	19.80	20.57
40.1 to < 70.1	91	81.7 ± 17.2	0.0001	13.01 ± 2.82	7.49	8.37	9.40	11.11	13.01	14.91	16.62	17.64	18.53	19.56
70.1 to ≤ 96	28	69.0 ± 7.8	0.443	10.00 ± 1.78	6.51	7.07	7.71	8.80	10.00	11.20	12.28	12.93	13.49	14.14

[a]Measured body weight. Normal-weight and overweight/obese females defined according to the body mass index (BMI) cut-offs. BMIs for sub-groups are reported in Table Web-8.

[b]Observed *p* values based on Shapiro-Wilk normality tests. Daily metabolic equivalent values are given in Table 19.

[c]Total daily energy requirements (TDERs) reported in Table Web-8 (in kcal/day) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG). TDEE = total daily energy expenditure (Table Web-7). ECG = stored daily energy cost for growth (Table Web-8). TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for 982 females aged 4 to 96 years (IOM 2002). ECGs from Table Web-1 were initially added to the basic TDEEs in order to obtain the TDER values.

[d]Percentiles based on a normal distribution assumption for all age groups. *n* =number of individuals; S.D.=standard deviation.

Tables Web-1, Web-7 and Web-8 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 18 Distribution percentiles of physiological daily inhalation rates (m^3/day-day) for free-living normal-weight and overweight/obese males aged 4 to 96 years

Male age group (years)	Observed *p* value[a]	Physiological daily inhalation rates[b] (m^3/kg-day)											DMET[d] (unitless)
		Mean ± S.D.	Percentile[c]										Mean ± S.D.
			2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th	
Normal-weight													
4 to < 5.1	0.132	0.418 ± 0.044	0.333	0.346	0.362	0.389	0.418	0.448	0.474	0.490	0.504	0.520	1.41 ± 0.13
5.1 to < 9.1	0.855	0.408 ± 0.057	0.296	0.314	0.335	0.369	0.408	0.446	0.481	0.502	0.520	0.540	1.52 ± 0.21
9.1 to <18.1	0.834	0.334 ± 0.048	0.240	0.255	0.272	0.302	0.334	0.366	0.395	0.413	0.428	0.445	1.68 ± 0.25
18.1 to < 40.1	0.073	0.245 ± 0.037	0.173	0.184	0.198	0.220	0.245	0.270	0.292	0.306	0.317	0.331	1.79 ± 0.22
40.1 to < 70.1	0.248	0.222 ± 0.040	0.143	0.155	0.170	0.195	0.222	0.249	0.274	0.289	0.301	0.316	1.68 ± 0.25
70.1 to ≤ 96	0.966	0.185 ± 0.032	0.122	0.132	0.144	0.163	0.185	0.206	0.226	0.237	0.247	0.259	1.52 ± 0.27
Overweight/obese													
4 to < 5.1	0.407	0.367 ± 0.044	0.281	0.295	0.310	0.337	0.367	0.396	0.423	0.439	0.453	0.469	1.44 ± 0.14
5.1 to < 9.1	0.002	0.345 ± 0.078	0.193	0.218	0.246	0.293	0.345	0.398	0.445	0.473	0.498	0.526	1.54 ± 0.29
9.1 to <18.1	0.755	0.265 ± 0.039	0.188	0.201	0.215	0.239	0.265	0.292	0.316	0.330	0.342	0.357	1.58 ± 0.17
18.1 to < 40.1	0.577	0.213 ± 0.036	0.142	0.154	0.167	0.189	0.213	0.237	0.259	0.272	0.284	0.297	1.84 ± 0.27
40.1 to < 70.1	0.053	0.194 ± 0.034	0.127	0.138	0.150	0.171	0.194	0.217	0.238	0.250	0.261	0.274	1.77 ± 0.29
70.1 to ≤ 96	0.504	0.173 ± 0.030	0.114	0.123	0.134	0.153	0.173	0.194	0.212	0.223	0.233	0.244	1.52 ± 0.28

[a]Observed *p* values based on Shapiro-Wilk normality tests. The number of individuals and measured body weight for normal-weight and overweight/obese males were gathered according to body mass index (BMI) cut-offs and are given in Table 16. BMIs for sub-groups are reported in Table Web-6.

[b]Total daily energy requirements (TDERs) reported in Table Web-6 (in kcal/kg-day) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG). TDEE = total daily energy expenditure (Table Web-5). ECG = stored daily energy cost for growth (Table Web-6). TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for 627 males aged 4 to 96 years (IOM 2002). ECGs from Table Web-1 were initially added to the basic TDEEs in order to obtain the TDER values.

[c]Percentiles based on a normal distribution assumption for all age groups.

[d]Daily metabolic equivalent or daily BEE multiplier (TDER/BEE). BEEs or basal energy expenditures (BMRs expressed on a 24-hour basis) were measured by indirect calorimetry (Table Web-5; IOM 2002).

Tables Web-1, Web-5 and Web-6 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 19 Distribution percentiles of physiological daily inhalation rates (m^3/day-day) for free-living normal-weight and overweight/obese females aged 4 to 96 years

Female age group (years)	Observed *p* value[a]	Physiological daily inhalation rates[b] (m^3/kg-day)											DMET[d] *(unitless)*
		Mean ± S.D.	Percentile[c]										Mean ± S.D.
			2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]	
Normal-weight													
4 to < 5.1	0.387	0.397 ± 0.048	0.304	0.319	0.336	0.365	0.397	0.430	0.459	0.476	0.491	0.508	1.42 ± 0.17
5.1 to < 9.1	0.086	0.372 ± 0.062	0.251	0.271	0.293	0.331	0.372	0.414	0.451	0.474	0.493	0.516	1.58 ± 0.24
9.1 to <18.1	0.300	0.290 ± 0.057	0.178	0.196	0.217	0.251	0.290	0.328	0.363	0.383	0.401	0.422	1.69 ± 0.30
18.1 to < 40.1	0.008	0.234 ± 0.038	0.160	0.172	0.186	0.209	0.234	0.260	0.283	0.296	0.308	0.322	1.81 ± 0.27
40.1 to < 70.1	0.312	0.203 ± 0.038	0.128	0.140	0.154	0.177	0.203	0.229	0.252	0.266	0.278	0.292	1.72 ± 0.30
70.1 to ≤ 96	0.003	0.163 ± 0.035	0.095	0.106	0.119	0.140	0.163	0.187	0.208	0.221	0.232	0.244	1.33 ± 0.27
Overweight/obese													
4 to < 5.1	0.780	0.340 ± 0.044	0.254	0.268	0.284	0.310	0.340	0.370	0.396	0.412	0.426	0.442	1.42 ± 0.14
5.1 to < 9.1	0.215	0.316 ± 0.067	0.185	0.207	0.231	0.271	0.316	0.361	0.402	0.426	0.447	0.472	1.56 ± 0.28
9.1 to <18.1	0.172	0.247 ± 0.049	0.151	0.167	0.184	0.214	0.247	0.280	0.309	0.327	0.342	0.360	1.72 ± 0.32
18.1 to < 40.1	0.834	0.189 ± 0.027	0.135	0.144	0.154	0.170	0.189	0.207	0.224	0.234	0.243	0.253	1.78 ± 0.23
40.1 to < 70.1	0.713	0.162 ± 0.030	0.102	0.112	0.123	0.141	0.162	0.182	0.201	0.212	0.221	0.232	1.62 ± 0.26
70.1 to ≤ 96	0.578	0.145 ± 0.025	0.096	0.104	0.113	0.128	0.145	0.163	0.178	0.187	0.195	0.205	1.41 ± 0.24

[a]Observed *p* values based on Shapiro-Wilk normality tests. The number of individuals and measured body weight for normal-weight and overweight/obese females were gathered according to body mass index (BMI) cut-offs and are given in Table 17. BMIs for sub-groups are reported in Table Web-8.

[b]Total daily energy requirements (TDERs) reported in Table Web-8 (in kcal/kg-day) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG). TDEE = total daily energy expenditure (Table Web-7). ECG = stored daily energy cost for growth (Table Web-8). TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for 982 females aged 4 to 96 years (IOM 2002). ECGs from Table Web-1 were initially added to the basic TDEEs in order to obtain the TDER values.

[c]Percentiles based on a normal distribution assumption for all age groups.

[d]Daily metabolic equivalent or daily BEE multiplier (TDER/BEE). BEEs or basal energy expenditures (BMRs expressed on a 24-hour basis) were measured by indirect calorimetry (Table Web-7; IOM 2002).

Tables Web-1, Web-7 and Web-8 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 20 Physiological daily inhalation rates for free-living adults from less affluent societies

Subjects	*n*	Age (years) Mean ± S.D.	Body weight[e] (kg) Mean ± S.D.	Physiological daily inhalation rate[f] (m^3/day)	(m^3/kg-day)	DMET[g] *(unitless)*
Males						
Sub-group A[a]	6	26.8 ± 4.4	55.0 ± 4.0	15.6	0.283	1.8
Sub-group B[a]	5	25.8 ± 4.1	58.4 ± 2.6	15.6	0.266	1.7
Sub-group C[b]	16	35.0 ± 1.0	61.6 ± 6.4	25.5	0.414	3.0
Females						
Sub-group D[c]	15	35.7 ± 6.8	54.1 ± 12.4	11.7	0.217	1.6
Sub-group E[d]	10	30.0 ± 2.6	49.4 ± 5.3	13.6	0.276	2.0
Sub-group F[d]	7	26.0 ± 3.4	50.2 ± 6.0	13.1	0.260	1.7

[a]Thin Chilean laborers. [b]Gambian laborers. [c]Guatemalan mothers. [d]Gambian farmers. [e]Measured body weight.
[f]Total daily energy requirements (TDERs) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG).
TDEE = total daily energy expenditure. ECG = stored daily energy cost for growth. TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods (Black *et al.* 1996).
[g]Daily metabolic equivalent or daily BEE multiplier (TDER/BEE). BEEs or basal energy expenditures (BMRs expressed on a 24-hour basis) were measured by indirect calorimetry (Black *et al.* 1996).
Body mass index values, BEEs, TDEEs, ECGs and TDERs are reported in Table Web-10, which is available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).
n =number of individuals; S.D. = standard deviation.

Table 21 Physiological daily inhalation rates for underweight free-living adult females with anorexia nervosa and for control sub-groups

Female sub-groups[a]	*n*	Age (years) Mean ± S.D.	Body weight[a] (kg) Mean ± S.D.	Physiological daily inhalation rate[b] (m^3/day)	(m^3/kg-day)	DMET[c] *(unitless)*
Women with anorexia nervosa						
Sub-group A	8	27.8 ± 5.2	43.0 ± 5.6	16.4	0.382	2.6
Sub-group B	6	24.5 ± 6.9	42.5 ± 9.4	11.2	0.263	2.0
Sub-group C	3	36.0 ± 10.8	40.6 ± 1.0	9.9	0.244	1.5
Control sub-groups						
Sub-group A	11	24.5 ± 4.2	57.5 ± 5.1	13.3	0.232	1.8
Sub-group B	6	24.8 ± 7.0	42.5 ± 9.4	11.2	0.264	1.5

[a]Measured body weight.

[b]Total daily energy requirements (TDERs) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG). TDEE = total daily energy expenditure. ECG = stored daily energy cost for growth. TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods (Black *et al.* 1996).

[c]Daily metabolic equivalent or daily BEE multiplier (TDER/BEE). BEEs or basal energy expenditures (BMRs expressed on a 24-hour basis) were measured by indirect calorimetry (Black *et al.* 1996).

Body mass index values, BEEs, TDEEs, ECGs and TDERs are reported in Table Web-11, which is available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

n =number of individuals; S.D. = standard deviation.

Table 22 Physiological daily inhalation rates for free-living athletes, explorers and soldiers during extreme physical activity

Subjects	*n*	Age (years) Mean ± S.D.	Body weight[d] (kg) Mean ± S.D.	Physiological daily inhalation rate[e] (m^3/day)	Physiological daily inhalation rate[e] (m^3/kg-day)	DMET[f] *(unitless)*
Male athletes						
Swimmers	5	19.8 ± 1.6	80.3 ± 7.2	23.2	0.289	2.2
Cyclists[a]	4	24 ± n.d.	68.4 ± n.d.	45.9	0.672	4.7
Cross-country skiers	4	26 ± 1.8	75.1 ± 4.9	41.2	0.549	3.5
Mountaineers[b]	3	35.3 ± 4.0	64.3 ± 8.6	19.8	0.309	2.4
Female athletes						
Swimmers	3	20.7 ± 1.5	67.8 ± 2.0	14.9	0.219	1.8
During rigorous training	4	25 ± n.d.	50.6 ± 3.2	19.8	0.391	2.8
In calorimeter	9	26 ± 3.3	52.4 ± 4.1	9.5	0.181	1.2
Runners during training	9	26 ± 3.3	51.6 ± 3.5	16.0	0.310	2.0
Cross-country skiers	4	25 ± 2.2	54.4 ± 5.1	24.8	0.456	2.8
Mountaineers[b]	2	37.5 ± 6.4	54.0 ± 1.4	16.2	0.301	2.0
Endurance runners	9	n.d. ± n.d.	55.3 ± 6.2	16.6	0.301	2.3
Male explorers [c]	2	38.2 ± 2.0	78.5 ± 9.2	44.8	0.570	4.5
Male soldiers						
Jungle training	4	22.5 ± 3.3	73.8 ± 8.9	27.3	0.369	2.7
Field training	14	27.1 ± 5.4	75.2 ± 5.7	19.7	0.262	1.9
Winter training	23	27.1 ± 3.8	79.8 ± 6.3	28.0	0.351	2.7
High mountain training	23	27.1 ± 3.8	79.8 ± 6.3	40.7	0.509	3.9
Base camp training	23	27.1 ± 3.8	79.8 ± 6.3	20.7	0.260	2.0
Active service	15	20 ± n.d.	70.7 ± 5.3	25.1	0.355	2.5
Arctic training	10	n.d. ± n.d.	77.0 ± 7.5	24.1	0.313	2.4

[a]Over the 21 days of the Tour de France. [b]On Mount Everest.

[c]In the first 20 days of sled hauling across the Arctic by adults aged 35.3 and 41 years. [d]Measured body weight.

[e]Total daily energy requirements (TDERs) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). TDER = (TDEE + ECG).
TDEE = total daily energy expenditure. ECG = stored daily energy cost for growth. TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods (Black *et al.* 1996).

[f]Daily metabolic equivalent or daily BEE multiplier (TDER/BEE). BEEs or basal energy expenditures (BMRs expressed on a 24-hour basis) were measured by indirect calorimetry (Black *et al.* 1996).

Body mass index values, BEEs, TDEEs, ECGs and TDERs are reported in Table Web-12, which is available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

n =number of individuals; S.D. = standard deviation.

CHAPITRE TROISIÈME :

3 Article II

Physiological daily inhalation rates for free-living pregnant and lactating adolescents and women aged 11 to 55 years, using data from doubly labeled water measurements for use in health risk assessment

PHYSIOLOGICAL DAILY INHALATION RATES FOR FREE-LIVING PREGNANT AND LACTATING ADOLESCENTS AND WOMEN AGED 11 TO 55 YEARS, USING DATA FROM DOUBLY LABELED WATER MEASUREMENTS FOR USE IN HEALTH RISK ASSESSMENT

Pierre Brochu[1, 2, 3], Jean-François Ducré-Robitaille[1] and Jules Brodeur[2]

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[1] Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi et de l'état de l'environnement, Service des avis et expertises scientifiques, gouvernement du Québec, édifice Marie-Guyart, 7e étage, 675, boulevard René-Lévesque Est, Québec, QC, G1R 5V7, Canada.

[2] Département de santé environnementale et santé au travail, Faculté de médecine, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, QC, H3C 3J7, Canada.

[3] To whom all correspondence should be addressed.

ABSTRACT

The distribution of physiological daily inhalation rates for pregnant and lactating females aged 11 to 55 years was determined according to total daily energy expenditures, energy costs for growth, pregnancy and lactation (maternal milk-energy synthesis and breast-energy output) in free-living females. Such published data were obtained using a methodology based on the disappearance rates of predetermined doses of doubly labeled water ($^{2}H_2O$ and $H_2{}^{18}O$) in urine from non-pregnant and non-lactating females (n=357), as well as saliva from gravid and breastfeeding females (n=91), monitored by gas-isotope-ratio mass spectrometry over an aggregate period of about 6 000 days. Monte Carlo simulations were necessary to integrate total daily energy requirements of non-pregnant and non-lactating females into energy costs and weight changes at the 9th, 22nd and 36th week of pregnancy and at the 6th and 27th postpartum week: 540 000 data were simulated. The present paper confirms that physiological daily inhalation rates for under-, normal- and overweight/obese pregnant and lactating females expressed in m^3/day and m^3/kg-day are higher than those for males. For instance, in normal-weight subjects, inhalation rates are higher by 18 to 41% throughout pregnancy and 23 to 39% during postpartum weeks: actual values were higher in females by 1.13 to 2.01 m^3/day at the 9th week of pregnancy, 3.74 to 4.53 m^3/day at the 22nd week and 4.41 to 5.20 m^3/day at the 36th week, and by 4.43 to 5.30 m^3/day at the 6th postpartum week and 4.22 to 5.11 m^3/day at the 27th postpartum week. The highest 99th percentiles were found to be 0.622 m^3/kg-day in pregnant females and 0.647 m^3/kg-day in lactating females. By comparison, the highest 99th percentile value for individuals aged 2.6 months to 96 years was determined to be 0.725 m^3/kg-day in Brochu *et al.* (2006a). Air quality criteria and standard calculations based on the latter value for non-carcinogenic toxic compounds should therefore be protective for virtually all pregnant and lactating females. The present paper highlights evidence that the current default assumption regarding the total daily air intake used by the Integrated Risk Information System (IRIS) to derive human equivalent concentrations in reference concentration calculations is also underestimated compared to some higher 75th and 90th percentiles of physiological daily inhalation rates in pregnant and lactating females.

Key words: daily inhalation rates, pregnancy, lactation, distribution percentiles, probability density functions, air quality criteria, standard value, risk assessment, doubly labeled water.

LIST OF MAIN ABBREVIATIONS

BEE: basal energy expenditure (BMR expressed on a 24-hour basis)

BMI: body mass index

BMR: basal metabolic rate (punctual measurement)

DLW: doubly labeled water

DMET: daily metabolic equivalent (TDER/BEE ratio)

ECG: stored daily energy cost for growth

H: oxygen uptake factor, volume of 0.21 L of oxygen (at standard temperature and pressure, dry air) consumed to produce 1 kcal of energy expended

MET: metabolic equivalent (BMR multiplier)

TDEE: total daily energy expenditure

TDER: total daily energy requirement (summation of ECG and TDEE)

V_E: minute volume rate

VO_2: oxygen uptake rate

VQ: ventilatory equivalent ratio (V_E at body temperature pressure saturation/VO_2 at standard temperature and pressure, dry air)

INTRODUCTION

Air pollution has been shown to be positively linked to adverse health outcomes in humans from infancy to advanced adulthood (see Brochu *et al.* 2006a). The intake of air pollutants by the respiratory tract is expected to be higher in males than in females, according to the main conclusions of a previous study: mean daily inhalation values for individuals aged 2.6 months to 96 years determined by using doubly labeled water (DLW) measurements were higher in males (n=746) than in females (n=1185) by 0.12 to 4.95 m^3/day and 0.002 to 0.032 m^3/kg-day (Brochu *et al.* 2006a). On the other hand, women live longer than men and have a higher percentage of body fat (Durnin and Passmore 1967). Lipophilic toxic chemicals absorbed into the body through air pollution are stored in fat tissue and may remain sequestered for years before being released into the general circulation (Arnay-De-La-Rosa *et al.* 1998; Aronson *et al.* 2000; Drasch *et al.* 1987; Grandjean 1988; Hu *et al.* 1991; Kosnett 1992; Landrigan 1991; Landrigan and Todd 1994; Liljegren *et al.* 1998; Silbergeld *et al.* 1993; Stellman *et al.* 2000; Wolff *et al.* 1993). For instance, lipophilic organochlorines stored in fats, such as dichlorodiphenyltrichloroethane and polychlorinated biphenyls are released at critical periods of life, notably during weight loss resulting from an energy-restricted diet or when hormonal change occurs during pregnancy, lactation and menopause (Demers *et al.* 2000; Dorgan *et al.* 1999; Hoyer *et al.* 2000, 2002; Lucena *et al.* 2001; Millikan *et al.* 2000; Moysich *et al.* 1998; Pelletier *et al.* 2002).

Other chemicals absorbed through air pollution, such as lead, are stored in bone tissue. The mobilization of lead from bone tissue into the bloodstream has been observed during pregnancy, lactation and menopause; it also increases in calcium-deficient diets (Arnest and Mahaffey, 1984; Bruening *et al.* 1999; Carbone *et al.* 1998; Cifuentes *et al.* 2000; Farias *et al.* 1996; Goldman *et al.* 1994; Goyer 1997; Grandjean 1988; Graziano *et al.* 1990; Han *et al.* 2000; Hernández-Avila *et al.* 1996, 1998; Hertz-Picciotto *et al.* 2000; Hu *et al.* 1991; Koren *et al.* 1990; Kostial *et al.* 1991; Landrigan 1991; Landrigan and Todd 1994; Levallois *et al.* 1991; Muldoon *et al.* 1994; O'Halloran *et al.* 1992; Rothenberg *et al.* 1996; Schell *et al.* 2003; Silbergeld 1991; Silbergeld *et al.* 1989, 1993). Lead released into the bloodstream is more pronounced in aging women than in their male counterparts (Chisholm 1987; Cory-Slechta 1990; Goldman *et al.* 1994; Kosnett 1992; Muldoon *et al.* 1994; Silbergeld *et al.* 1989). Most chemicals found in the bloodstream of pregnant women may be transferred to the embryos or fetus by the umbilical cord after crossing the placenta during pregnancy, or transferred to newborns during breastfeeding in the postpartum phase (Scialli 1992). In fact, numerous epidemiological studies have confirmed links between air pollutants and adverse birth outcomes in humans, such as low birth weight, premature birth and infant mortality (Bobak 2000; Bobak and Leon 1999; Bobak *et al.* 2001; Dejmek *et al.* 1999; Ha *et al.* 2001; Liu *et al.* 2003; Loomis *et al.* 1999; Maisonet *et al.* 2001; Ritz and Yu 1999; Ritz *et al.* 2000; Rogers *et al.* 2000; Wang *et al.* 1997; Woodruff *et al.* 1997, 2003; Xu *et al.* 1995).

Punctual experimental lung function measurements suggest that daily inhalation rates increase during pregnancy and postpartum weeks (Wolfe *et al.* 1998). During pregnancy, breathing is deeper and is more diaphragmatic than thoracic (Ciliberto and Marx 1998). The minute ventilation rate at rest progressively increases soon after conception, as early as 7 or 8 weeks of gestation, and peaks up at 50% above pregravid levels around the second trimester, primarily due to a 40% increase in the tidal volume and a 15% increase in the respiratory frequency (Artal *et al.* 1986; Ciliberto and Marx 1998; Clapp *et al*. 1988; Edwards *et al.* 1981; Field *et al.* 1991; Knuttgen and Emerson 1974; Pernoll *et al.* 1975; Prowse and Gaensler 1965; Rees *et al.* 1990; Wolfe *et al.* 1998). Minute ventilation rates (V_E) at rest and during steady-state exercise are definitely greater during pregnancy and values increase progressively throughout gestation, peaking at term (Artal and O'Toole 2003; Edwards *et al.* 1981; Field *et al.* 1991; Knuttgen and Emerson 1974; Ohtake and Wolfe 1998; Pernoll *et al.* 1975; Pivarnik *et al.* 1992; Wolfe *et al.* 1998). This increase of the minute ventilation rate compensates for a loss of functional residual capacity and a 10 to 20% increase in oxygen consumption in response to the needs of the growing fetus (Ciliberto and Marx 1998; Edwards *et al.* 1981; Field *et al.* 1991; Knuttgen and Emerson 1974; Pivarnik *et al.* 1992; Sady *et al.* 1989; Wolfe *et al.* 1998). Since physiological dead space remains unchanged, alveolar ventilation is about 70% higher at the end of gestation (Ciliberto and Marx 1998; Pivarnik *et al.* 1992; Prowse and Gaensler 1965; Sady *et al.* 1989).

Energetic data related to free-living individuals also show that reproduction is very demanding on the female metabolism, which in turn increases metabolic oxygen consumption (Butte *et al.* 1997, 1999, 2001, 2003, 2004; Durnin *et al.* 1987; Forsum *et al*. 1988, 1992; Goldberg *et al.* 1991, 1993; King 2000; King *et al.* 1994; Kopp-Hoolihan *et al.* 1999; Lovelady *et al*. 1993; Piers *et al.* 1995; Prentice *et al.* 1996a, 1996b; Prentice and Prentice 1988; Prentice and Whitehead 1987; Sadurskis *et al.* 1988; Singh *et al.* 1989; Spaaij *et al.* 1994; Thongprasert *et al.* 1987; Tuazon *et al.* 1987; van Raaij *et al*. 1987, 1991). Within several weeks of conception, the placenta is secreting hormones that affect the metabolism of all nutrients (King 2000; Prentice *et al.* 1994b; Prentice and Goldberg

2000). Such adjustments in nutrient metabolism, in addition to changes in the anatomy and physiology of the pregnant female, support fetal growth and development while maintaining maternal homeostasis and preparing for lactation, which corresponds to the most energy-demanding phase of the human reproductive cycle (Butte *et al.* 1997; King 2000).

The DLW method allows for an accurate understanding of the energy balance in human beings from birth to advanced adulthood (Brochu *et al.* 2006a; Butte *et al*. 2004; IDECG 1990; Lucas 1989; Prentice and Goldberg, 2000). Using the DLW method, total daily energy expenditures (TDEEs) for pregnant and lactating females can be determined according to the disappearance rates of an oral dose of doubly labeled water (^2H_2O and $H_2{}^{18}O$), deuterium (^2H) and heavy oxygen-18 (^{18}O) being monitored in saliva, blood or urine samples by gas-isotope-ratio mass spectrometry over a long period of time – from 7 to 21 days for each subject under normal free-living conditions in their normal surroundings (IDECG 1990; IOM 2002; Lucas 1989; Torun *et al.* 1996). For instance, additional overall energy costs for two pregnant female groups have been measured by the DLW method as totalizing 91 614 ± 29 904 kcal (n=10) and 99 726 ± 83 025 kcal (n=12) over the complete gestational period (Goldberg *et al.* 1993; King 2000; Kopp-Hoolihan *et al.* 1999). In late pregnancy, approximately half of the increment in a TDEE of 302 kcal/day is required by the fetus. The fetus uses 55.8 kcal $kg^{-1}d^{-1}$, which would be equivalent to 168 kcal/day for a 3-kg fetus (Butte *et al.* 1999; Sparks 1980). In addition, the total energy cost for maternal breastfeeding, which includes the metabolism of milk synthesis (106 kcal/day) and milk energy outputs (477 to 539 kcal/day), is higher than the total energy cost (32 and 496 kcal/day) for pregnancy (Butte *et al.* 2001, 2004; Goldberg *et al.* 1991; IOM 2002). Basically, each additional kcal of energy expended during pregnancy and the postpartum phase compared to baseline values for non-pregnant and non-lactating females requires an extra average metabolic consumption of 0.21 liter of oxygen (Layton 1993). To reach the same volume of oxygen uptake (VO_2), pregnant and lactating females inhale more air than their non-gravid and non-lactating counterparts (Wolfe *et al.* 1998). The ventilatory equivalent at rest and during steady-state exercise (V_E/VO_2 ratio) varies from 30.5 to 36.8 during pregnancy and from 26.5 to 36.4 during postpartum, compared to the recognized value of 27 for non-gravid and non-lactating females (Cugell *et al.* 1953; Knuttgen and Emerson 1974; Layton 1993; Pernoll *et al.* 1975). The higher oxygen uptake measured in pregnant females, which is justified by the fetus oxygenation (≈8 mL O_2 $kg^{-1}min^{-1}$), contributes to an increase of the respiratory drive during pregnancy (Butte *et al.* 1999; Knuttgen and Emerson 1974; Wolfe *et al.* 1998). Because of the increased oxygen requirements at rest and the increased difficulty in breathing caused by pressure of the enlarged uterus on the diaphragm, there is less oxygen available for the performance of aerobic exercise during pregnancy (Artal *et al.* 1986; Artal and O'Toole 2003; Clapp 1990; Heenan *et al.* 2001; Pivarnik *et al.* 1990).

In brief, DLW data and lung function measurements both suggest that daily inhalation rates in gravid and lactating females are higher than the baseline values for their non-pregnant and non-lactating counterparts. Higher respiratory drive during the reproductive cycle thus increases the risk of air pollution intake. This contributes to an increase in the uptake of chemicals into maternal blood, in addition to the mobilization of different environmental pollutants from fats and bones. Besides, there is no study in current scientific literature on the determination of daily inhalation rates for pregnant and lactating females. In order to fulfill this lack of essential information in health risk assessment, the present paper is intended to determine the distribution of physiological daily inhalation rates for pregnant and lactating adolescents and women aged 11 to 55 years based on DLW measurements, both extreme age limits reflecting possible physiologically functioning ovarian activity (Guyton 1991; Hermann-Giddens *et al.* 1997; IOM 1990; Moore *et al.* 1992).

RELEVANT METHODOLOGICAL APPROACHES

Study Design and Subjects

The present study was designed to calculate physiological daily inhalation rates (expressed in m^3/day and m^3/kg-day) for underweight, normal-weight and overweight/obese females aged 11 to 55 years in prepregnancy, at weeks 9, 22 and 36 during pregnancy and weeks 6 and 27 postpartum, based on DLW measurements. Additional sets of physiological values were similarly determined for normal-weight males in the same age group for comparison purposes with normal-weight female inhalation values. Age groups (years) are: 11 to less than 23; 23 to less than 30; 30 to 55. In each age group, data are classified into three sub-groups according to BMI cutoffs settled by the IOM (1990) for prepregnant females in order to obtain a desirable gestational weight gain and deposition of maternal fat and, associated with the best outcome for both infants, in terms of birth weight, and mothers, in terms of delivery complications and postpartum weight retention. Underweight, normal-weight, and overweight/obese individuals are defined as those having BMIs lower than 19.8 kg/m^2, between 19.8 and 26 kg/m^2 and greater than 26 kg/m^2 respectively (IOM 1990).

TDEEs and bodyweights for free-living individuals (n=488) aged 11 to 55 years based on DLW measurements have been used to determine total daily energy requirements (TDERs) for underweight (n=81), normal-weight (n=172), overweight/obese (n=104) non-pregnant and non-lactating females (Table Web-1; MDDEP 2006) and for normal-weight males as a control group (Table Web-2; n=131). The energy cost for growth was initially added to the basic TDEEs in order to obtain the appropriate TDERs for males aged 11 to 24 years as well as non-pregnant and non-lactating females aged 11 to 18 years (Brochu *et al*. 2006a). All TDERs and bodyweights of the cohort of non-pregnant and non-lactating females aged 11 to 55 years (n=357) have been used to determine baseline weight (Tables Web-5 to Web-7) and energetic (Tables Web-8 to Web-13) values for 45 000 prepregnant (day zero of pregnancy) females by Monte Carlo simulations. Energetic cost and bodyweight variations during pregnancy and lactation measured in adult females by the DLW method until delivery and during postpartum weeks (Tables Web-3 and Web-4) have been integrated by Monte Carlo simulations to the baseline values of these 45 000 pregnant females in order to obtain TDERs and bodyweights at the 9th, 22nd and 36th week of pregnancy and at the 6th and 27th postpartum week. Means, standard deviations and percentiles of energetic values in kcal/day and kcal/kg-day for males (Table Web-2) and females (Tables Web-1 and Web-8 to Web-13) were converted into physiological daily inhalation rates in m^3/day (Tables 14 to 18) and m^3/kg-day (Tables 14, 15 and 19 to 21) by using the equation developed by Layton (1993).

Data Selection

Punctual bodyweight (in kg), basal metabolic rate (BMR in kcal/day) and TDEE (in kcal/day) measurements for each free-living male and female subject based on the DLW method are available in IOM (2002). As it will be discussed later, measured data including TDEE values in Butte *et al.* (2004) were appropriate to characterize the energy cost and gestational weight gain at the 9th, 22nd and 36th week of pregnancy, as well as the weight loss at the 6th and 27th postpartum week. Also, breast-energy outputs reported in the IOM (2002) and energy costs for milk synthesis determined by Goldberg *et al.* (1991), according to TDEE measurements, were preferentially used to determine the total daily energy cost for lactation. All TDEE values were based on the DLW method.

Doubly Labeled Water Method

The DLW method measures carbon dioxide (CO_2) production for up to 3 weeks following the simultaneous ingestion of predetermined doses of doubly labeled water (^2H_2O and $H_2{}^{18}O$). The disappearance of deuterium (^2H) and heavy oxygen-18 (^{18}O) from the body in urine, saliva or blood is measured in samples collected from free-living individuals over a long period of time – from 7 to 21 days using isotope ratio mass spectrometry. The concentration of deuterium (^2H) decreases as a result of dilution in the body: 1) from unlabelled water consumed every day (in food and drink); 2) by the addition of metabolic water produced as a result of nutrient oxidation; and 3) by the loss of labeled water via evaporation and excretion. The heavy oxygen (^{18}O) is lost mostly as oxygen in the water molecule, and partly as oxygen in the CO_2 molecule that is expired. Some of the ^{18}O is seen in carbonic acid, or the bicarbonate formed by the dissolving of CO_2 in body water. However, ^{18}O is free to interchange between water and CO_2 through the action of carbonic anhydrase, which yields a rapid equilibration of body water and bicarbonate pools. The decrease in ^{18}O in the body water is a measure for H_2O plus CO_2 outputs, whereas the decrease in ^2H is a measure for H_2O output alone. Hence the CO_2 output can be calculated by the difference. Energy expenditure can then be calculated by knowing the respiratory quotient (IDECG 1990; Lucas 1989). The accuracy of the DLW method assessed by different validation studies varies by about ±5% (IDECG 1990; IOM 2002; Lucas 1989; Torun *et al.* 1996). Disappearance rates of deuterium and heavy oxygen-18 for free-living females in prepregnancy (n=357) and for males (n=131), reported in IOM (2002), were monitored in urine samples for a duration varying between 7 to 21 days per subject. In Butte *et al.* (2004), isotopic forms of water (^2H_2O and $H_2{}^{18}O$) were monitored in saliva samples of free-living prepregnant and pregnant females (n=63). Once a baseline saliva value was established, a daily saliva sample was collected during the next 13 days for each female for analytical measurement by gas-isotope-ratio mass spectrometry. Daily milk, urine and saliva samples were analyzed during an aggregate period of about 6 000 days.

Physiological Daily Inhalation Calculations

Distribution percentiles of TDERs (in kcal/day and kcal/kg-day) for males, females in prepregnancy as well as pregnant and lactating females were converted into physiological daily inhalation rates, using the equation from Layton (1993):

PDIR = $(TDER * H * VQ*10^{-3})$ Equation 1

Where,

PDIR = physiological daily inhalation rate (m^3/day)

TDER = total daily energy requirement for pregnant and lactating females (kcal/day)

H = oxygen uptake factor, volume of 0.21 L of oxygen (at standard temperature and pressure, dry air or STPD) consumed to produce 1 kcal of energy expended

VQ = ventilatory equivalent ratio of the minute volume (V_E at body temperature pressure saturation or BTPS) to the oxygen uptake rate (VO_2 at standard temperature and pressure, dry air)

10^{-3} = conversion factor (L/m^3)

Mean VQ values at 19-22, 23-36, 27-30, 31-34, 35-38 and 39-42 weeks of pregnancy and at 2-4, 5-8, 12-14 and 25-50 postpartum weeks were calculated by Pernoll *et al.* (1975) based on 480 measurements of V_E at BTPS and VO_2 at STPD (240 measured values each) in 12 adult females at rest and during steady-state exercise at 306 kpm/min on a bicycle ergometer. Among the calculated VQ values, the value of 36.8 is used in the present paper to calculate physiological daily inhalation rates at the 9th and 22nd week of pregnancy, while the value of 36.2 is used at the 36th week (Pernoll *et al.* 1975). Similarly, VQ values of 34.5 and 34.2 are used at the 6th and 27th postpartum week, respectively (Pernoll *et al.* 1975). Such VQ values are consistent with other published data (Cugell *et al.* 1953; Knuttgen and Emerson 1974; Wolfe *et al.* 1998). It was not appropriate to use the slightly lower VQ values measured by Pernoll *et al.* (1975) during steady-state exercise. In the case of gravid and breastfeeding females, overstrain and overwork are usually avoided. This is done by reducing physical activity and increasing work efficiency by adjusting daily physical activities (Butte *et al.* 1997, 1999, 2001, 2004; Golberg *et al.* 1991; Poppitt *et al.* 1993, 1994; Prentice *et al.* 1989, 1994a, 1994b; Prentice and Prentice 1988; Spaaij, 1993; Spaaij *et al.* 1994; Thongprasert *et al.* 1987; van Raaij *et al.* 1987). VQ of 27 is used for the calculation of the daily inhalation rates for males and for females at prepregnancy (Layton 1993).

Energy Cost for Growth

The growth process is completed for females and males at age 18 and 24 respectively. For their younger counterparts, the energy cost for growth must be added to each TDEE in order to obtain the adequate corresponding TDER (Brochu *et al*. 2006a). The energy cost for growth in females aged 11 to 18 years corresponds to an increase of 4.2% of the TDEEs. In males aged 11 to less than 13 years, 13 to 20 years and at the ages of 21, 22, 23 and 24 years, the energy cost for growth corresponds to an increase of 3.0%, 4.2%, 3.3%, 2.5%, 1.7% and 0.8% of the TDEE respectively (Brochu *et al*. 2006a; n=93).

Energy Cost during Pregnancy

Total daily energy costs (in kcal/day) measured at the 9th, 22nd and 36th week of pregnancy by Butte *et al.* (2004) for adult females aged 21 to 39 years (n=63) with low-, medium- and high-BMI values (< 19.8, 19.8 to 26.0 and > 26.1 kg/m^2 respectively) were added to the TDEE of each female during prepregnancy (n=357) in order to establish TDERs for underweight, normal-weight and overweight/obese pregnant females. The mean (±SD) daily energy cost for pregnancy compared to baseline values for pregravid females were 137 ± 368, 163 ± 512 and 294 ± 602 kcal/day in the low-BMI group (n=17), 32 ± 461, 356 ± 416 and 496 ± 368 kcal/day in the normal-BMI group (n=34), and 367 ± 585, 441 ± 755 and 434 ± 806 kcal/day in the high-BMI group (n=12), at the 9th, 22nd and 36th week of pregnancy respectively (Table Web-3; MDDEP 2006). Butte *et al.* (2004) improved the traditional methodologies used to determine energy costs for pregnancy and lactation by jointly using the DLW method, highly precise room respiration calorimeters and body composition measurements. Thus, the BMR is measured by calorimetry, and the TDEE by the DLW method. The TDEE is capturing the BMR, activity energy expenditure and thermic effect of food (IDECG 1990). Activity energy expenditures are deduced based on TDEE and BMR values (as TDEE – BMR). Energy deposition is calculated from changes in body protein and fat. TDER is the sum of TDEE and daily energy deposition.

Components of the energy balance (i.e. order of magnitude of BMR, TDEE values, activity energy expenditures) among pregnant females with similar body fatness or BMI values vary according to their initial physical condition in prepregnancy (baseline TDEE and physical activity levels) and their capacity to save energy by adjusting their physical activity, increasing work efficiency and by the change in their metabolic response to food (Butte *et al.* 1999; Prentice *et al*. 1989; Thongprasert *et al.* 1987; van Raaij *et al* 1987). Results in Butte *et al.* (2004) for low-, medium- and high-BMIs are extremely consistent with the results reported in other longitudinal studies: increments in BMR over prepregnancy values (2 to 34%) are similar to other published data (2 to 35.4%), while TDEEs increase more modestly because of higher baseline physical activity levels (3 to 13% by the third trimester) compared to other published data (1 to 26%) using the DLW method, room calorimetry or other approaches (Butte *et al.* 1999; de Groot *et al.*1994; Forsum *et al.*1988, 1992; Goldberg *et al.* 1991, 1993; Kopp-Hoolihan *et al*. 1999; Prentice *et al.* 1989; Spaaij, 1993; van Raaij *et al.* 1987).

Energy Cost during Lactation

The total energy cost during lactation may be supplied for by increasing food intake, mobilizing body fat reserves, reducing energy expenditure (decreasing activity) or increasing metabolic efficiency (Butte *et al.* 1997, 2001, 2004; Golberg *et al.* 1991; Prentice *et al.* 1996a; Prentice and Prentice 1988). A decrease of BMRs in lactating females was also reported (Blackburn and Calloway 1976; Guillermo-Tuazon *et al.* 1992; Lawrence *et al.* 1986; van Raaij *et al.* 1991). However, in general, it appears that the BMR during lactation is unchanged (Butte *et al.* 1997; Butte *et al.* 2001; Goldberg *et al.* 1991; Illingworth *et al.* 1986; Madhavapeddi and Rao1992; Motil *et al.* 1990; Schutz *et al.* 1980; Singh *et al.* 1989; van Raaij *et al.* 1991) or slightly elevated (Butte *et al.* 1999; Forsum et al. 1992, Sadurskis *et al.* 1988; Spaaij *et al.* 1994). For some lactating women, energy requirements during lactation may be met by a reduction in the TDEE, caused largely by a reduction in physical activity (Butte *et al.* 1997, 2001; Golberg *et al.* 1991).

Breast-energy output

In Butte *et al.* (2004), milk was also analyzed for energy content by adiabatic bomb calorimetry. Mean milk energy outputs of 530 ± 302, 33 ± 472 and 276 ± 497 kcal/day for women (n=63) with BMIs less than 19.8 kg/m^2, between 19.8 and 26 kg/m^2 and higher than 26 kg/m^2 respectively were measured at 27 weeks postpartum. At the 2nd, 6th, and 27th postpartum week, 55, 53, and 39 of the 63 women, respectively, were breastfeeding. Yet, by the end of the 27th week, only 62% of the women were breastfeeding their infants. The mean milk energy output in women (n=6) who exclusively breastfed their infants was 531 kcal/day, compared to 413 kcal/day in women (n=33) who partially breastfed their children (Butte *et al.* 2004). A mean breast-milk output of 481.3 ± 78.7 kcal/day was also measured by Butte *et al.* (2001) for mothers aged 30.4 ± 3.2 years (n=24) during exclusive breastfeeding at 3 months postpartum. Their mean BMI at prepregnancy was 22.1 ± 3.1 kg/m^2, while the BMI during lactation was 23.5 ± 3.5 kg/m^2. The latter BMI value falls between medium- and high-BMI groups with a 97.5th percentile value of 30.3 kg/m^2. A higher mean energy output of 539.29 ± 106.26 kcal/day is reported in IOM (2002) for lactating mothers aged 26 to 40 years (31.0 ± 3.9 years; n=28), with BMI values between the low- and medium-BMI groups and ranging between 18.5 and 23.7 kg/m^2 (21.4 ± 1.8 kg/m^2). Such mean energy outputs expressed per sub-groups according the lactation period decreased throughout postpartum months, although too scarce to establish a clear statistic trend: 568.3 ± 93.0 (n=8), 531.7± 115.9 (n=9) and 524.5 ± 112.8 (n=11) in the 1st, the 2nd and between the 3rd and the 7th month of lactation respectively. In Butte *et al.* (1990), the mean maternal milk energy output of 477.4 kcal/day (n=10) at the 4th month postpartum was only slightly lower than the value of 483.8 kcal/day (n=10) at the 1st month of lactation. Considering the limited data for each BMI group depending on postpartum duration, the higher milk energy parameter of 539.29 ± 106.26 kcal/day was used in the present paper in order to determine safer physiological daily inhalation rates for use in health risk assessment (Table Web-4; MDDEP 2006).

Human milk synthesis

The TDEE, and especially the BMR, encompassed for the continuous process of human milk synthesis is not subject to feedback inhibition due to engorgement (Butte *et al.* 1997; Goldberg *et al.*1991; Prentice and Prentice 1988; Prentice *et al.* 1996a). However, the increase of milk synthesis beyond the BMR energy-sparing capacity requires an extra energy cost of about 106-110 kcal/day (Goldberg *et al.*1991; Prentice *et al.* 1996a). In Goldberg *et al.* (1991), an additional 106 kcal/day (or extra 20% of the milk energy output) was necessary for milk synthesis in lactating women (n=29) in order to provide a breast-energy output averaging 525 kcal/day over 12 postpartum weeks based on

29 breast-energy output measurements obtained from 10 lactating females. In Prentice *et al.* (1996a), the extra energy cost of about 110 kcal/day was estimated for the unavoidable metabolic milk synthesis (or around 10% of the BMR) when there is no energy-sparing adaptation in lactating females at 3 months postpartum. Extra energy cost of 107.86 ± 21.25 kcal/day for milk synthesis considering the possibility of no energy-sparing mechanisms in lactating females is retained in the present paper: 20% of the energy of 539.29 ± 106.26 kcal/day transferred in milk outputs (Table Web-4; MDDEP 2006).

Relevant values

The energy cost value for lactation used in the present paper for milk synthesis and breast-energy output is thus 647.14 ± 127.51 kcal/day. This value is consistent with current energetic measurements in well-nourished women during postpartum (n=204) relative to baseline values: extra food energy intake from 358.7 to 583.1 kcal/day, energy mobilization of body fat reserves from -23.9 to -286.3 kcal/d and aggregate data on energy transferred in milk which varies from 477.4 to 539.3 kcal/day (Butte *et al.* 1990, n=10; Butte *et al.* 1997, n=40; Butte *et al.* 1999, n=40; Butte *et al.* 2001, n=24; Butte *et al.* 2004, n=6; Forsum *et al.* 1992, n=23; Goldberg *et al.* 1991, n=10; IOM 2002, n=28; Lovelady *et al.* 1993, n=9; Singh *et al.* 1989, n=14).

Weight Variations during Pregnancy and Postpartum

Weight gain during pregnancy results from products of conception (fetus, placenta and amniotic fluid), increases in various maternal tissues (uterus, breasts, blood and extracellular extravascular fluid) and increases in maternal fat stores (Butte *et al.* 2004;

Prentice and Goldberg, 2000). Day-to-day variations of bodyweight (gain and loss) measured by Butte *et al.* (2004) for the same cohort of females (n=63) throughout pregnancy and postpartum weeks were used in the present paper. Gestational weight gains measured by Butte *et al.* (2004) at the 9^{th}, 22^{nd} and 36^{th} week of pregnancy and at the end of gestation were added to the bodyweight of prepregnant females (Table Web-3; MDDEP 2006). Gradually, weight loss was determined according to measurements from Butte *et al*. (2004) at the 2^{nd}, 6^{th} and 27^{th} postpartum weeks (Table Web-4). Mean gestational weight gain throughout pregnancy and weight loss during postpartum weeks measured by Butte *et al.* (2004) are consistent with those reported in IOM (1990).

Gestational weight gain

The mean gestational period is 38.3 ± 1.6, 39.3 ± 1.1 and 39.6 ± 1.2 weeks in the low-, normal-, and high-BMI groups respectively. The total mean gestational weight gain, computed as the difference in weight at delivery minus baseline, is 15.0 ± 3.8, 14.5 ± 4.5, and 17.9 ± 5.4 kg, including mean fat gains of 5.3, 4.6 and 8.4 kg for women in the low-, normal- and high-BMI groups. The mean daily gestational weight gain is 33.0 ± 42.1, 6.8 ± 46.6 and 68.1± 69.1 g/day from the 1^{st} to the 9^{th} week, 66.8 ± 18.7, 52.7 ± 19.6 and 71.0 ± 31.5 g/day from the 9^{th} to the 22^{nd} week, and 53.7 ± 20.6, 81.5 ± 21.3 and 83.2 ± 37.7 g/day from the 22^{nd} to the 36^{th} week in low-, normal- and high-BMI groups respectively (Table Web-3; MDDEP 2006).

Postpartum weight loss

Mean weight losses of 10.5, 10.01 and 11.30 kg from delivery to the 6^{th} postpartum week are measured in lactating females with low-, normal- and high-BMI values respectively.

Those weight losses include products of conception (fetus, placenta and amniotic fluid), maternal fat and mean birth weights which are 3.38 ± 0.44, 3.55 ± 0.39, and 3.82 ± 0.47 kg in the low-, normal- and high-BMI groups respectively. Maternal weight losses specifically measured from the 2nd to the 6th postpartum week are –11.9 ± 41.3, –23.4 ± 55.9 and –26.6 ± 53.2 g/day, while they are –17.3 ± 13.8, –15.5 ± 20.0 and –14.4 ± 25.3 g/day from the 6th to the 27th postpartum week for the low-, normal- and high-BMI groups, respectively (Table Web-4; MDDEP 2006).

Statistics

Means and standard deviations of BMIs, bodyweights, basal energy expenditure (BMR expressed on a 24-hour basis), energy cost for growth, TDEEs, TDERs (in kcal/day and kcal/kg-day) and daily metabolic equivalents (MET or physical activity levels) were calculated for each sub-group of males as well as non-pregnant and non-lactating females. The distribution of physiological daily inhalation rates (in m^3/day and m^3/kg-day) and the associated statistical *p* values based on the Shapiro-Wilk normality tests were also calculated for those male and female sub-groups. Means, standard deviations and distribution of bodyweight percentiles as well as TDERs (in kcal/day and kcal/kg-day) were calculated for females at the 9th, 22nd and 36th week of pregnancy and at the 6th and 27th postpartum week by using Monte Carlo simulations. Physiological daily inhalation rates (in m^3/day and m^3/kg-day) were then calculated by using the equation of Layton (1993).

Monte Carlo simulations

TDER distribution percentiles for males as well as for non-pregnant and non-lactating females were calculated assuming normality, a hypothesis adequately justified by the observed *p* values of the Shapiro-Wilk normality tests. Input energetic and bodyweight measurements for non-pregnant and non-lactating females as well as the ones for pregnant and lactating females were integrated by using Monte Carlo simulations. Each female was randomly chosen in a specific analyzed sub-group. For each one, energetic evolution as a function of time was determined by simulating her TDER and bodyweight changes at conception (0 week of pregnancy) and at the 9^{th}, 22^{nd} and 36^{th} week of pregnancy as well as at the 6^{th} and 27^{th} postpartum week based on appropriate input physiological measurement statistics. This was repeated 5000 times for each sub-group of under-, normal- and overweight/obese groups at prepregnancy and throughout the pregnancy and postpartum weeks, for a total of 540 000 simulated data in kcal/day and kcal/kg-day (108 sets of 5000 energetic data) pertaining to 45 000 simulated subjects (Tables Web-5 to Web-13; MDDEP 2006). TDER differences for pregnancy including the energy cost for gravid status were simulated with a lognormal distribution (justified by the large standard deviations reported in Butte *et al.* 2004), while the ones for breastfeeding females during postpartum, which include the milk-energy synthesis and the breast-energy output, were simulated with a normal distribution (Tables Web-8 to Web-13). Weight changes during pregnancy and postpartum weeks were also simulated using a normal distribution (Tables Web-5 to Web-7). Since no information is available about weight auto-correlation in time and the correlation between weight and TDER, independence is assumed for the simulation. This can lead to a greater variability of the estimated weight and TDER values, but not necessarily when TDERs are expressed per unit of bodyweight (Tables Web-11 to Web-13).

Bootstrap statistical technique

The bootstrap statistical technique was used to estimate bodyweight and TDER percentiles (in kcal/day and kcal/kg-day) for simulated females in all sub-groups since some initial small population sizes (4 out of 9; $14 \leq n \leq 25$) imposed minimal and maximal observed measurements as stable values at some lower and upper percentiles respectively. For instance, since there are only 17 observed TDER values for the underweight female adults aged 23 to less than 30 years, percentile values higher than the 94^{th} percentile (ratio 16/17 = 0.941) were all equal to the maximal value of 3529 kcal/day (Table Web-8). With the bootstrap method, the 95^{th}, 97.5^{th} and 99^{th} percentiles of 3141, 3447 and 3522 kcal/day respectively were estimated considering the maximal experimental TDER of 3529 kcal/day from the initial sample as being the 100^{th} percentile (Table Web-8; MDDEP 2006). For consistency purposes, this technique was used for all sub-populations of each BMI sub-group without any exception, even for simulated data from larger baseline samples (5 out of 9; $50 \leq n \leq 64$) which were leading to a lower statistical impact on percentiles. The bootstrap technique allows for a smooth distribution by simulating a number of samples of a specified size from a specified population, calculating the relevant percentiles each time and finally averaging them. For each sub-population of under-, normal- and overweight/obese groups at the 9^{th}, 22^{nd} and 36^{th} week of pregnancy as well as at the 6^{th} and 27^{th} postpartum week, data from 100 subjects were randomly selected among data from 5000 simulated subjects. A first set of relevant percentiles (2.5^{nd}, 5^{th}, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th, 99th) was calculated, and then those 100 data were reintegrated into the sub-groups. The procedure was repeated 100 times in order to obtain 100 sets of relevant percentiles, the average of which lead to the final distribution associated to each sub-population.

RESULTS AND STATISTICAL ANALYSIS

Tables Web-1 to Web-13 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web Site (MDDEP 2006) and may be consulted in English at: http://www.mddep.gouv.qc.ca/air/inhalation/index-en.htm, or in French at: http://www.mddep.gouv.qc.ca/air/inhalation/index.htm. Further information can also be obtained by contacting the authors. Tables 14 to 21 are part of the present paper. Physiological baseline measurements for males as well as non-pregnant and non-lactating females (bodyweights, BMIs, BEEs, TDEEs, energy cost for growth and TDERs) are presented in Tables Web-1 and Web-2. Means and standard deviations of measurements for daily energy costs (kcal/day) and gestational weight gains (mg/day) during pregnancy are reported in Table Web-3. Daily energy costs for lactating females and their weight losses during postpartum weeks are shown in Table Web-4. Bodyweight means, standard deviations and distribution percentiles for under-, normal- and overweight/obese pregnant and lactating females are given in Tables Web-5, Web-6 and Web-7 respectively. Similar measured statistic values for TDERs expressed in kcal/day during pregnancy and postpartum weeks for under-, normal- and overweight/obese females are reported in Tables Web-8, Web-9 and Web-10 respectively, while those expressed in kcal/kg-day are presented in Tables Web-11, Web-12 and Web-13 respectively. Means, standard deviations and distribution percentiles of physiological daily inhalation rates for males as well as non-pregnant and non-lactating females with the associated statistical observed *p* values are reported in Tables 14 and 15 respectively. Means, standard deviations and distribution percentiles of physiological daily inhalation rates for under-, normal- and overweight/obese females during prepregnancy (0 week of pregnancy), at the 9^{th}, 22^{nd} and 36^{th} week of pregnancy as well as at the 6^{th} and 27^{th} postpartum week are presented in Tables 16 to 18 (in m^3/day) and Tables 19 to 21 (in m^3/kg-day).

The distribution of physiological daily inhalation rates (in m^3/day and m^3/kg-day) for normal-weight males (Table 14) and under-, normal- and overweight/obese non-pregnant and non-lactating females (Table 15) were calculated assuming normality for each sub-group of individuals. That assumption was adequately justified by the results of Shapiro-Wilk normality tests ($p \geq 0.05$): *p* values were higher than 0.05 for 5 sub-groups out of 6 in males (Table 14) and for 17 sub-groups out of 18 in females (Table 15). Other *p* values (2 out of 24) also remain higher or equal to 0.01 (0.01 and 0.042). Moreover, comparisons of means, standard deviations as well as percentiles of physiological daily inhalation rates are biologically consistent between sub-groups for each gender, and between normal-weight female and male values (Tables 14 to 15). A small difference is observed between statistics (means, standard deviations and percentiles) of prepregnancy female sub-groups (at 0 week of pregnancy) and physiological baseline measurements of the initial experimental sub-populations of non-pregnant and non-lactating females, since each subject does not have exactly the same mathematical weight in each sub-population of BMI sub-groups. However, bodyweight and TDER percentiles for each sub-population of prepregnancy females that have been randomly estimated by Monte Carlo simulations are similar to those based on normal distribution for each associated baseline sub-population of non-pregnant and non-lactating females.

DISCUSSION

As observed in Brochu *et al.* (2006a), mean physiological daily inhalation rates calculated in the present paper for normal-weight males (Table 14: 17.01 ± 2.53 to 18.86 ± 2.85 m^3/day, 0.234 ± 0.035 to 0.279 ± 0.043 m^3/kg-day, n=131) are higher than those for normal-weight non-pregnant and non-lactating females (Table 15: 13.82 ± 1.91 to 14.55 ± 2.70 m^3/day, 0.184 ± 0.031 to 0.277 ± 0.046 m^3/kg-day, n=172). However, mean physiological daily inhalation rates for normal-weight females during pregnancy (19.00 ± 9.98 to 23.27 ± 4.63 m^3/day) and postpartum phase (21.96 ± 3.02 to 23.28 ± 3.60 m^3/day) become in turn higher than normal-weight male values by 6 to 12% at the 9th week, 20 to 27% at the 22nd week, and 23 to 31% at the 36th week of pregnancy, and by 23 to 31% at the 6th week and 22 to 30% at the 27th week postpartum (Tables 14 and 17). Mean daily rates expressed per unit of bodyweight (Tables 14 and 20) for normal-weight gravid (0.297 ± 0.056 to 0.360 ± 0.085 m^3/kg-day) females are also higher than those for their male counterparts by 23 to 34% at the 9th week, 29 to 41% at the 22nd week, and 18 to 29% at the 36th week of pregnancy (Table 20). The increase of mean volumes of air in m^3/kg-day inhaled by females throughout pregnancy, with the lower values at the 36th week of pregnancy compared to higher values at the 9th and 22nd week, is definitely non-linear and physiologically consistent with the increase of gestational weight gains which nearly peaks during the third trimester and the slightly lower VQ value of 34.2 also during the third trimester compared to 36.8 in the two first trimesters (Pernoll *et al.* 1975; Wolfe *et al.* 1998). As found in the literature, lactation corresponds to the most energy-demanding phase of the human reproductive cycle (Butte *et al.* 1997; King, 2000). High energy costs for breastfeeding (milk-energy synthesis and breast-energy outputs) associated with weight losses throughout postpartum weeks lead to the expected higher physiological daily inhalation rates by the lactating females (0.309 ± 0.045 to 0.352 ± 0.067 m^3/kg-day) compared to male baselines by 23 to 35% at the 6th week and 26 to 39% at the 27th week postpartum (Table 20), despite a lower VQ value of 34.2 at the 27th week compared to 34.5 at the 6th week (Pernoll *et al.* 1975; Wolfe *et al.* 1998). Almost all (297 out of 300) percentiles (2.5nd, 5th ,10th, 25th, 50th, 75th, 90th, 95th, 97.5th and 99th) of physiological daily inhalation rates (in m^3/day and m^3/kg-day) for normal weight pregnant and lactating females are higher than the ones for normal-weight males (Tables 14, 17 and 20).

Mean physiological daily inhalation rates of underweight (12.18 ± 2.08 to 13.93 ± 2.27 m^3/day, 0.249 ± 0.027 to 0.277 ± 0.046 m^3/kg-day; n=81) and overweight/obese (15.45 ± 2.32 to 16.62 ± 2.91 m^3/day, 0.184 ± 0.031 to 0.206 ± 0.033 m^3/kg-day; n=104) non-pregnant and non-lactating females (Table 15) also increase to higher values throughout pregnancy and postpartum weeks. Daily inhalation rates of gravid underweight and overweight/obese females vary from 17.83 ± 4.52 to 20.91 ± 5.37 m^3/day (0.301 ± 0.074 to 0.385 ± 0.011 m^3/kg-day) and 23.93 ± 5.94 to 26.10 ± 6.96 m^3/day (0.242 ± 0.068 to 0.302 ± 0.075 m^3/kg-day) respectively (Tables 16, 18, 19 and 21). Those values increase during postpartum weeks to daily rates, ranging from 20.21 ± 2.66 to 22.45 ± 2.91 m^3/day (0.337 ± 0.038 to 0.383 ± 0.064 m^3/kg-day) and from 24.25 ± 3.02 to 25.93 ± 3.70 m^3/day (0.253 ± 0.048 to 0.285 ± 0.053 m^3/kg-day) for underweight and overweight/obese breastfeeding females respectively (Tables 16, 18, 19 and 21). The

99th percentiles of physiological daily inhalation rates for underweight (25.07 to 38.26 m^3/day; 0.489 to 0.647 m^3/kg-day), normal-weight (28.75 to 35.88 m^3/day; 0.443 to 0.594 m^3/kg-day) and overweight/obese (30.81 to 47.31 m^3/day; 0.404 to 0.521 m^3/kg-day) pregnant and lactating females (Tables 16 to 21) are higher than all those that are reported in Brochu et *al.* (2006a) for males with BMIs lower than 19.8 and greater than 26 kg/m^2 when involved in normal free-living activities. The 99th percentile values for individuals aged 11 to less than 40 years varied from 22.70 to 28.81 m^3/day (0.297 to 0,410 m^3/kg-day, $0.030 \leq p \leq 0.986$, n=157), whereas the values for individuals 40 to 96 years varied from 18.72 to 26.59 m^3/day (0.244 to 0.328 m^3/kg-day; $0.053 \leq p \leq 0.967$, n=196). Observed p values in Brochu et *al.* (2006a) were also based on Shapiro-Wilk normality tests.

The highest physiological daily inhalation percentiles of 0.622 m^3/kg-day in pregnant females and 0.647 m^3/kg-day in lactating females determined in the present study are higher than the daily inhalation rate of 0.444 m^3/kg-day used by Health Canada (1996) to calculate the tolerable daily intake for non-carcinogenic compounds. They are also higher than the daily inhalation rates for individuals aged less than 1 year up to 18 years (0.21 to 0.59 m^3/kg-day) based on single values of Layton (1993) that are recommended in United States as long-term inhalation rates and for long-term dose assessment of air pollutants (USEPA, 1996, 1997, 2000; Versar, 2000). Daily rates for females and males aged between 12 and 18 years notably vary from 0.21 to 0.24 m^3/kg-day and 0.26 to 0.30 m^3/kg-day respectively (Layton 1993). Moreover, 296 percentiles of physiological daily inhalation rates out of 450 for pregnant and lactating females are higher than the value of 0.286 m^3/kg-day (i.e. 20 m^3/day for a 70-kg adult male) adopted as a standard value for humans in the United States by the Federal Register (1980) and which is still used in health risk assessment. Moreover, in order to calculate reference concentrations, the default assumption that the total respiratory tract surface area of an adult human male (54.3 m^2) is exposed to a total daily air intake of 20 m^3 is used by the Integrated Risk Information System (IRIS) of the United States Environmental Protection Agency to derive human equivalent concentrations (HECs) based on animal exposure to particles and reactive gases that elicit respiratory effects (Benson *et al*. 2002). However, based on the present paper, approximately one pregnant or lactating female out of two is exposed to a total daily air intake of 20 m^3 up to the highest 99th percentile of 47.3 m^3 (Tables 16 to 18).

CONCLUSION

Our findings based on DLW measurements in free-living individuals confirm that physiological daily inhalation rates for pregnant and lactating females are higher than those for under-, normal- and overweight/obese males. Thus, daily inhalation values expressed in m^3/kg-day for males will not provide adequate protection in health risk assessment for pregnant and lactating females. According to comparisons between mean values for normal-weight individuals, the evaluated intake of air pollutants by the respiratory tract would be underestimated by 18 to 41% in pregnant females and 23 to 39% in lactating females. The present paper highlights evidence that the current default assumption regarding the total daily air intake used by IRIS to derive HEC values in reference concentration calculations is also underestimated compared to some higher 75th and 90th percentiles of physiological daily inhalation rates in pregnant and lactating females. Moreover, intakes of non-carcinogenic and carcinogenic air pollutants are also expected to be higher in pregnant and breastfeeding females than in males as well as in non-gravid and non-lactating females. Perera *et al.* (2004) showed that prenatal exposure to carcinogens apparently results in differentially higher levels of procarcinogenic DNA damage in fetus. In certain individuals, it may disproportionately increase the probability of developing a cancer over their lifetime.

In the future, reference values for daily inhalation rates used in health risk assessment for gravid and breastfeeding females should take into consideration the findings of the present study, namely the highest 99^{th} percentile value of 0.647 m^3/kg-day (Table 19). By comparison, the highest 99^{th} percentile value for individuals aged 2.6 months to 96 years was determined to be 0.725 m^3/kg-day in Brochu *et al.* (2006a). Air quality criteria and standard calculations based on the latter value for non-carcinogenic toxic compounds should therefore be protective for virtually all pregnant and lactating females.

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Table 14 Distribution of physiological daily inhalation rate percentiles for free-living normal-weight males aged 11 to 55 years for comparison purposes with female values

Age group[a] (years)	Observed p value[b]	Physiological daily inhalation rates[c]										
		Mean ± S.D.	Percentile[d]									
			2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
			(m^3/day)									
11 to < 23	0.611	18.86 ± 2.85	13.28	14.17	15.21	16.94	18.86	20.78	22.50	23.54	24.44	25.48
23 to < 30	0.296	17.43 ± 2.73	12.07	12.93	13.93	15.59	17.43	19.27	20.93	21.92	22.78	23.79
30 to 55	0.109	17.01 ± 2.53	12.05	12.85	13.77	15.30	17.01	18.72	20.25	21.17	21.97	22.89
			(m^3/kg-day)									
11 to < 23	0.144	0.279 ± 0.043	0.194	0.208	0.224	0.250	0.279	0.308	0.334	0.350	0.364	0.380
23 to < 30	0.227	0.243 ± 0.036	0.173	0.184	0.197	0.219	0.243	0.267	0.288	0.301	0.312	0.325
30 to 55	0.010	0.234 ± 0.035	0.165	0.176	0.189	0.210	0.234	0.258	0.279	0.292	0.303	0.316

[a]Normal-weight males are defined in Table Web-1 according to body mass index cutoffs for females varying between 19.8 and 26 kg/m^2 associated with the best outcome for both infants, in terms of birth weight, and mothers, in terms of delivery complications and postpartum weight retention (IOM 1990).

[b]Observed p values based on Shapiro-Wilk normality tests.

[c]Calculated by converting TDERs reported in Table Web-4 into inhalation rates. Physiological daily inhalation rates = TDER*H*(V_E/VO_2)*10^{-3}, where H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27. TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure. The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine were monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods for 131 males aged 11 to 55 years (Brochu *et al.* 2006a; Butte 2000; Butte *et al.* 2000; Layton 1993; Rogol *et al*. 2000; IOM 2002).

[d]Percentiles based on a normal distribution assumption for all age groups. S.D. = standard deviation.

Tables Web-1 and Web-4 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 15 Distribution of physiological daily inhalation rate percentiles for free-living non-pregnant and non-lactating adolescents and women aged 11 to 55 years

Weight status[a] and age group (years)	Observed p value[b]	Physiological daily inhalation rates[c]										
		Mean ± S.D.	Percentile[d]									
			2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
			(m³/day)									
Underweight												
11 to < 23	0.989	12.18 ± 2.08	8.11	8.76	9.52	10.78	12.18	13.58	14.84	15.60	16.25	17.02
23 to < 30	0.042	13.93 ± 2.27	9.49	10.20	11.02	12.40	13.93	15.45	16.83	17.65	18.37	19.20
30 to 55	0.472	12.89 ± 1.40	10.14	10.58	11.09	11.94	12.89	13.84	14.69	15.20	15.64	16.16
Normal-weight												
11 to < 23	0.188	14.55 ± 2.70	9.26	10.11	11.09	12.73	14.55	16.37	18.01	18.99	19.84	20.83
23 to < 30	0.700	13.59 ± 2.23	9.22	9.92	10.73	12.09	13.59	15.09	16.45	17.26	17.96	18.78
30 to 55	0.175	13.82 ± 1.91	10.07	10.67	11.37	12.53	13.82	15.12	16.28	16.97	17.58	18.28
Overweight/obese												
11 to < 23	0.065	16.62 ± 2.91	10.90	11.82	12.88	14.65	16.62	18.58	20.35	21.41	22.33	23.39
23 to < 30	0.567	15.45 ± 2.32	10.89	11.63	12.47	13.88	15.45	17.02	18.43	19.27	20.00	20.86
30 to 55	0.220	15.87 ± 2.52	10.92	11.72	12.63	14.17	15.87	17.57	19.10	20.01	20.81	21.73
			(m³/kg-day)									
Underweight												
11 to < 23	0.178	0.277 ± 0.046	0.187	0.201	0.218	0.246	0.277	0.308	0.335	0.352	0.366	0.383
23 to < 30	0.096	0.264 ± 0.047	0.171	0.186	0.203	0.232	0.264	0.296	0.325	0.342	0.357	0.374
30 to 55	0.922	0.249 ± 0.027	0.196	0.204	0.214	0.231	0.249	0.267	0.283	0.293	0.302	0.312
Normal-weight												
11 to < 23	0.556	0.252 ± 0.051	0.152	0.168	0.186	0.217	0.252	0.286	0.317	0.336	0.352	0.370
23 to < 30	0.172	0.221 ± 0.035	0.153	0.164	0.176	0.197	0.221	0.244	0.265	0.278	0.289	0.301
30 to 55	0.514	0.229 ± 0.035	0.160	0.171	0.184	0.206	0.229	0.253	0.274	0.287	0.298	0.311
Overweight/obese												
11 to < 23	0.525	0.206 ± 0.033	0.141	0.151	0.163	0.184	0.206	0.229	0.249	0.261	0.272	0.284
23 to < 30	0.666	0.186 ± 0.025	0.136	0.144	0.153	0.169	0.186	0.203	0.218	0.227	0.235	0.244
30 to 55	0.607	0.184 ± 0.031	0.122	0.132	0.144	0.163	0.184	0.205	0.224	0.235	0.245	0.257

[a]Underweight, normal-weight and overweight/obese female status as defined in Table Web-1 according to BMI cutoffs associated with the best outcome for both infants, in terms of birth weight, and mothers, in terms of delivery complications and postpartum weight retention.
[b]Observed p values based on Shapiro-Wilk normality tests.
[c]Calculated by converting TDERs reported in Table Web-1 into inhalation rates. Physiological daily inhalation rates = TDER*H*(V_E/VO_2)*10^{-3}, where H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27. TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure. The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine were monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods for 357 females aged 11 to 55 years (Brochu *et al.* 2006a; Butte 2000; Butte *et al.* 2000; Layton 1993; Rogol *et al*. 2000; IOM 2002).
[d]Percentiles based on a normal distribution assumption for all age groups. S.D. = standard deviation.
Table Web-1 is available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 16 Distribution of physiological daily inhalation rate (m^3/day) percentiles for free-living underweight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks.

Age group (years)	Progression of the reproductive cycle	Number of subjects[b] $n_{Exp.}$ or $n_{Sim.}$	Mean ± S.D.	2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
			Physiological daily inhalation rates[c] (m^3/day)	Percentile									
11 to < 23	Non-pregnant females	50	12.18 ± 2.08	8.11	8.76	9.52	10.78	12.18	13.58	14.84	15.60	16.25	17.02
	Prepregnancy 0 week	5000	12.27 ± 1.95	8.98	9.35	9.74	10.79	12.18	13.72	14.63	15.48	16.23	16.90
	Pregnancy 9th week	5000	17.83 ± 4.52	12.71	13.20	13.91	15.40	17.34	19.55	21.38	23.13	25.09	27.40
	Pregnancy 22nd week	5000	17.98 ± 4.77	12.70	13.19	13.95	15.47	17.46	19.73	22.09	23.90	26.66	30.69
	Pregnancy 36th week	5000	18.68 ± 4.73	12.91	13.44	14.25	15.96	17.88	20.24	23.01	25.59	29.40	34.45
	Postpartum 6th week	5000	20.39 ± 2.69	15.84	16.31	17.02	18.47	20.31	22.22	23.79	24.82	25.80	26.62
	Postpartum 27th week	5000	20.21 ± 2.66	15.70	16.17	16.88	18.31	20.14	22.02	23.58	24.61	25.57	26.39
23 to < 30	Non-pregnant females	17	13.93 ± 2.27	9.49	10.20	11.02	12.40	13.93	13.93	16.83	17.65	18.37	19.20
	Prepregnancy 0 week	5000	13.91 ± 2.17	11.38	11.41	11.50	12.08	13.92	15.32	16.01	17.81	19.54	19.97
	Pregnancy 9th week	5000	20.03 ± 5.01	15.71	15.83	16.17	17.08	19.75	21.60	23.76	26.94	29.14	34.21
	Pregnancy 22nd week	5000	20.15 ± 4.24	15.71	15.81	16.16	17.07	19.80	21.67	24.49	27.46	29.62	32.69
	Pregnancy 36th week	5000	20.91 ± 5.37	15.73	15.97	16.37	17.56	20.29	22.31	26.42	28.95	32.33	38.26
	Postpartum 6th week	5000	22.45 ± 2.91	18.37	18.70	19.15	20.14	22.23	24.15	25.65	27.68	29.61	30.57
	Postpartum 27th week	5000	22.25 ± 2.89	18.21	18.53	18.98	19.96	22.04	23.94	25.42	27.44	29.35	30.30
30 to 55	Non-pregnant females	14	12.89 ± 1.40	10.14	10.58	11.09	11.94	12.89	12.89	14.69	15.20	15.64	16.16
	Prepregnancy 0 week	5000	12.91 ± 1.36	10.71	10.85	11.28	11.99	12.49	13.98	14.99	15.13	15.18	15.18
	Pregnancy 9th week	5000	18.68 ± 3.95	14.92	15.33	15.93	16.79	18.05	20.22	21.39	22.69	24.45	27.38
	Pregnancy 22nd week	5000	18.84 ± 4.08	14.93	15.30	15.93	16.80	18.07	20.23	21.52	23.20	26.03	30.80
	Pregnancy 36th week	5000	19.60 ± 4.66	15.12	15.54	16.14	17.03	18.73	20.74	23.04	25.58	28.80	34.26
	Postpartum 6th week	5000	21.19 ± 1.96	17.88	18.30	18.86	19.79	20.92	22.58	23.98	24.53	24.94	25.28
	Postpartum 27th week	5000	21.01 ± 1.94	17.73	18.14	18.69	19.62	20.74	22.39	23.77	24.31	24.72	25.07

[a]Underweight females are defined as those having a body mass index lower than 19.8 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Resulting TDERs from the integration of energetic measurements in underweight non-pregnant and non-lactating females (IOM, 2002; n=81) with those during pregnancy (Butte *et al*. 2004; n=17) and lactation (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by Monte Carlo simulations (Table Web-8) were converted into physiological daily inhalation rates by the following equation: TDER*H*(V_E/VO_2)*10^{-3}. TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure.The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine or saliva samples were monitored by gaz-isotope-ratio mass spectrometry for a 7 to 21-day period per subject. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 for non-pregnant, non-lactating and prepregnant females (Layton 1993). During pregnancy V_E/VO_2 = 36.8 at the 9th and 22nd week and 36.2 at the 36th week. During postpartum, V_E/VO_2 = 34.5 and 34.2 for breastfeeding mothers at the 6th and 27th postpartum week respectively (Pernoll *et al.* 1975).

Tables Web-1 and Web-8 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 17 Distribution of physiological daily inhalation rate (m^3/day) percentiles for free-living normal-weight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	*Number of subjects*[b] *n E xp. or n Sim.*	Mean ± S.D.	Physiological daily inhalation rates[c] (m^3/day) Percentile 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females	57	14.55 ± 2.70	9.26	10.11	11.09	12.73	14.55	16.37	18.01	18.99	19.84	20.83
	Prepregnancy 0 week	5000	14.55 ± 2.69	8.88	9.71	10.83	13.29	14.78	15.89	17.34	18.71	20.02	20.91
	Pregnancy 9th week	5000	19.99 ± 3.89	12.23	13.32	14.84	18.32	20.26	21.86	23.86	25.89	27.80	28.75
	Pregnancy 22nd week	5000	22.59 ± 4.83	14.08	15.35	17.09	20.06	22.27	24.69	28.25	30.75	33.35	35.88
	Pregnancy 36th week	5000	23.27 ± 4.63	14.73	16.01	17.76	20.69	23.10	25.55	28.77	31.07	33.17	35.65
	Postpartum 6th week	5000	23.28 ± 3.60	15.85	16.91	18.36	21.40	23.56	25.24	27.17	28.98	30.70	31.80
	Postpartum 27th week	5000	23.08 ± 3.56	15.71	16.76	18.20	21.21	23.36	25.02	26.93	28.73	30.43	31.52
23 to < 30	Non-pregnant females	54	13.59 ± 2.23	9.22	9.92	10.73	12.09	13.59	15.09	16.45	17.26	17.96	18.78
	Prepregnancy 0 week	5000	13.66 ± 2.29	9.70	10.19	10.64	12.12	13.73	14.90	16.49	17.87	18.57	19.09
	Pregnancy 9th week	5000	19.00 ± 9.98	13.35	13.92	14.55	16.55	18.76	20.49	22.80	24.49	25.46	27.04
	Pregnancy 22nd week	5000	21.36 ± 4.36	14.76	15.54	16.70	18.63	20.89	23.58	26.59	28.43	30.58	33.98
	Pregnancy 36th week	5000	22.14 ± 4.13	15.43	16.21	17.34	19.35	21.69	24.55	27.59	29.27	30.93	32.77
	Postpartum 6th week	5000	22.15 ± 3.05	16.69	17.37	18.26	20.11	22.11	23.96	26.21	27.53	28.48	29.21
	Postpartum 27th week	5000	21.96 ± 3.02	16.54	17.22	18.10	19.93	21.91	23.75	25.98	27.29	28.23	28.96
30 to 55	Non-pregnant females	61	13.82 ± 1.91	10.07	10.67	11.37	12.53	13.82	15.12	16.28	16.97	17.58	18.28
	Prepregnancy 0 week	5000	13.79 ± 1.83	10.82	11.07	11.48	12.54	13.61	14.91	16.40	17.02	17.55	18.32
	Pregnancy 9th week	5000	19.02 ± 3.81	14.80	15.18	15.74	17.14	18.63	20.46	22.45	23.38	24.46	27.39
	Pregnancy 22nd week	5000	21.53 ± 4.06	16.19	16.71	17.56	19.01	20.85	23.45	26.03	28.30	30.63	33.44
	Pregnancy 36th week	5000	22.20 ± 3.68	16.87	17.45	18.19	19.69	21.73	24.16	26.78	28.53	30.53	32.75
	Postpartum 6th week	5000	22.31 ± 2.50	18.20	18.72	19.35	20.58	22.09	23.84	25.70	26.70	27.56	28.39
	Postpartum 27th week	5000	22.12 ± 2.48	18.04	18.55	19.18	20.40	21.90	23.64	25.47	26.47	27.32	28.14

[a]Normal-weight females are defined as those having a body mass index varying between 19.8 and 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Resulting TDERs from the integration of energetic measurements in normal-weight non-pregnant and non-lactating females (IOM, 2002; n=172) with those during pregnancy (Butte *et al.* 2004; n=34) and lactation (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by Monte Carlo simulations (Table Web-9) were converted into physiological daily inhalation rates by the following equation: TDER*H*(V_E/VO_2)*10^{-3}. TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure. The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine or saliva samples were monitored by gaz-isotope-ratio mass spectrometry for a 7 to 21-day period per subject. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 for non-pregnant, non-lactating and prepregnant females (Layton 1993). During pregnancy V_E/VO_2 = 36.8 at the 9th and 22nd week and 36.2 at the 36th week. During postpartum, V_E/VO_2 = 34.5 and 34.2 for breastfeeding mothers at the 6th and 27th postpartum week respectively (Pernoll *et al.* 1975).

Tables Web-1 and Web-9 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 18 Distribution of physiological daily inhalation rate (m^3/day) percentiles for free-living overweight/obese[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle		Number of subjects[b] $n_{E xp.}$ or $n_{Sim.}$	Physiological daily inhalation rates[c] (m^3/day) Mean ± S.D.	Percentile 2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females		15	16.62 ± 2.91	10.90	11.82	12.88	14.65	16.62	18.58	20.35	21.41	22.33	23.39
	Prepregnancy	0 week	5000	16.64 ± 2.81	9.68	10.21	12.13	15.52	17.22	18.52	19.68	20.06	20.14	20.16
	Pregnancy	9th week	5000	25.51 ± 6.48	14.90	16.11	19.09	23.04	25.38	27.85	30.62	33.32	36.77	41.61
	Pregnancy	22nd week	5000	26.10 ± 6.96	14.98	16.38	19.29	23.12	25.65	28.17	31.56	34.93	39.08	45.94
	Pregnancy	36th week	5000	25.71 ± 8.09	14.35	15.67	18.78	22.73	25.23	27.84	31.14	34.95	40.06	46.76
	Postpartum	6th week	5000	25.93 ± 3.70	17.03	17.94	20.12	24.52	26.61	28.38	29.87	30.53	30.93	31.27
	Postpartum	27th week	5000	25.71 ± 3.67	16.88	17.79	19.94	24.30	26.38	28.13	29.61	30.26	30.66	31.00
23 to < 30	Non-pregnant females		25	15.45 ± 2.32	10.89	11.63	12.47	13.88	15.45	17.02	18.43	19.27	20.00	20.86
	Prepregnancy	0 week	5000	15.47 ± 2.27	10.42	11.94	13.12	14.36	15.50	16.86	17.96	19.46	20.23	20.41
	Pregnancy	9th week	5000	23.93 ± 5.94	15.72	17.75	19.13	21.08	23.22	25.62	29.09	31.77	35.37	40.74
	Pregnancy	22nd week	5000	24.44 ± 6.24	16.03	18.06	19.45	21.32	23.51	26.44	29.92	33.49	37.83	44.56
	Pregnancy	36th week	5000	24.15 ± 6.82	15.61	17.60	19.00	20.91	23.05	26.02	30.04	34.18	39.34	47.31
	Postpartum	6th week	5000	24.47 ± 3.04	17.60	19.31	21.07	22.80	24.45	26.16	27.93	29.43	30.38	31.08
	Postpartum	27th week	5000	24.25 ± 3.02	17.45	19.14	20.88	22.60	24.23	25.93	27.68	29.17	30.12	30.81
30 to 55	Non-pregnant females		64	15.87 ± 2.52	10.92	11.72	12.63	14.17	15.87	17.57	19.10	20.01	20.81	21.73
	Prepregnancy	0 week	5000	15.83 ± 2.46	11.30	11.92	12.79	14.30	15.79	17.19	18.78	19.47	20.35	22.03
	Pregnancy	9th week	5000	24.47 ± 5.68	16.97	17.87	19.17	21.38	23.77	26.37	29.77	33.08	36.37	41.49
	Pregnancy	22nd week	5000	25.02 ± 6.65	17.08	18.13	19.41	21.44	23.92	26.93	30.98	35.01	39.10	46.88
	Pregnancy	36th week	5000	24.46 ± 6.24	16.71	17.67	18.83	20.92	23.40	26.37	30.32	34.27	38.68	45.08
	Postpartum	6th week	5000	24.91 ± 3.28	18.90	19.82	20.92	22.82	24.91	26.81	28.70	29.75	30.91	32.94
	Postpartum	27th week	5000	24.70 ± 3.25	18.74	19.65	20.74	22.63	24.69	26.58	28.45	29.50	30.65	32.65

[a]Overweight/obese females are defined as those having a body mass index higher than 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Resulting TDERs from the integration of energetic measurements in overweight/obese non-pregnant and non-lactating females (IOM, 2002; n=104) with those during pregnancy (Butte *et al.* 2004; n=12) and lactation (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by Monte Carlo simulations (Table Web-10) were converted into physiological daily inhalation rates by the following equation: $TDER*H*(V_E/VO_2)*10^{-3}$. TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure. The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine or saliva samples were monitored by gaz-isotope-ratio mass spectrometry for a 7 to 21-day period per subject. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 for non-pregnant, non-lactating and prepregnant females (Layton 1993). During pregnancy V_E/VO_2 = 36.8 at the 9th and 22nd week and 36.2 at the 36th week. During postpartum, V_E/VO_2 = 34.5 and 34.2 for breastfeeding mothers at the 6th and 27th postpartum week respectively (Pernoll *et al.* 1975).

Tables Web-1 and Web-10 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 19 Distribution of physiological daily inhalation rate (m^3/kg-day) percentiles for free-living underweight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	*Number of subjects* [b] *n E xp. or n Sim.*	Physiological daily inhalation rates[c] (m^3/kg-day) Mean ± S.D.	Percentile 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females	50	0.277 ± 0.046	0.187	0.201	0.218	0.246	0.277	0.277	0.335	0.352	0.366	0.383
	Prepregnancy 0 week	5000	0.276 ± 0.045	0.205	0.209	0.218	0.238	0.277	0.313	0.337	0.345	0.356	0.368
	Pregnancy 9th week	5000	0.385 ± 0.110	0.269	0.278	0.291	0.327	0.377	0.428	0.474	0.504	0.545	0.622
	Pregnancy 22nd week	5000	0.343 ± 0.093	0.239	0.246	0.259	0.291	0.335	0.378	0.419	0.455	0.505	0.602
	Pregnancy 36th week	5000	0.323 ± 0.083	0.222	0.230	0.243	0.274	0.314	0.357	0.404	0.452	0.506	0.575
	Postpartum 6th week	5000	0.368 ± 0.058	0.309	0.321	0.337	0.370	0.414	0.467	0.517	0.548	0.571	0.596
	Postpartum 27th week	5000	0.383 ± 0.064	0.316	0.329	0.348	0.383	0.433	0.491	0.549	0.584	0.615	0.647
23 to < 30	Non-pregnant females	17	0.264 ± 0.047	0.171	0.186	0.203	0.232	0.264	0.264	0.325	0.342	0.357	0.374
	Prepregnancy 0 week	5000	0.264 ± 0.046	0.204	0.206	0.212	0.228	0.257	0.284	0.342	0.361	0.362	0.362
	Pregnancy 9th week	5000	0.366 ± 0.098	0.270	0.277	0.287	0.311	0.351	0.400	0.468	0.501	0.531	0.591
	Pregnancy 22nd week	5000	0.332 ± 0.076	0.243	0.250	0.260	0.282	0.318	0.362	0.421	0.452	0.483	0.532
	Pregnancy 36th week	5000	0.317 ± 0.086	0.227	0.233	0.242	0.266	0.301	0.346	0.402	0.439	0.488	0.582
	Postpartum 6th week	5000	0.352 ± 0.056	0.297	0.307	0.320	0.348	0.385	0.431	0.486	0.518	0.547	0.573
	Postpartum 27th week	5000	0.364 ± 0.061	0.305	0.316	0.330	0.357	0.397	0.449	0.508	0.545	0.579	0.606
30 to 55	Non-pregnant females	14	0.249 ± 0.027	0.196	0.204	0.214	0.231	0.249	0.249	0.283	0.293	0.302	0.312
	Prepregnancy 0 week	5000	0.249 ± 0.026	0.203	0.208	0.220	0.232	0.242	0.268	0.286	0.294	0.298	0.299
	Pregnancy 9th week	5000	0.347 ± 0.075	0.270	0.279	0.291	0.311	0.337	0.370	0.405	0.431	0.466	0.529
	Pregnancy 22nd week	5000	0.315 ± 0.071	0.244	0.252	0.262	0.280	0.305	0.335	0.368	0.401	0.448	0.529
	Pregnancy 36th week	5000	0.301 ± 0.074	0.226	0.233	0.243	0.260	0.287	0.321	0.360	0.404	0.461	0.529
	Postpartum 6th week	5000	0.337 ± 0.038	0.302	0.312	0.326	0.347	0.376	0.408	0.439	0.457	0.472	0.489
	Postpartum 27th week	5000	0.349 ± 0.042	0.309	0.320	0.333	0.357	0.389	0.425	0.462	0.483	0.500	0.518

[a]Underweight females are defined as those having a body mass index lower than 19.8 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Resulting TDERs from the integration of energetic and weight measurements in underweight non-pregnant and non-lactating females (IOM, 2002; n=81) with those during pregnancy (Butte *et al* . 2004; n=17) and lactation (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by Monte Carlo simulations (Table Web-11) were converted into physiological daily inhalation rates by the following equation: TDER*H*(V_E/VO_2)*10^{-3}. TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure. The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine or saliva samples were monitored by gaz-isotope-ratio mass spectrometry for a 7 to 21-day period per subject. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 for non-pregnant, non-lactating and prepregant females (Layton 1993). During pregnancy V_E/VO_2 = 36.8 at the 9th and 22nd week and 36.2 at the 36th week. During postpartum, V_E/VO_2 = 34.5 and 34.2 for breastfeeding mothers at the 6th and 27th week postpartum postpartum respectively (Pernoll *et al.* 1975).

Tables Web-1 and Web-11 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 20 Distribution of physiological daily inhalation rate (m^3/kg-day) percentiles for free-living normal-weight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	Number of subjects[b] $\underline{n}_{Exp.}$ or $n_{Sim.}$	Physiological daily inhalation rates[c] (m^3/kg-day) Mean ± S.D.	Percentile 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females	<u>57</u>	0.252 ± 0.051	0.152	0.168	0.186	0.217	0.252	0.286	0.317	0.336	0.352	0.370
	Prepregnancy 0 week	5000	0.252 ± 0.051	0.159	0.169	0.189	0.218	0.246	0.282	0.324	0.339	0.354	0.361
	Pregnancy 9th week	5000	0.344 ± 0.074	0.218	0.232	0.259	0.297	0.336	0.388	0.440	0.468	0.489	0.518
	Pregnancy 22nd week	5000	0.360 ± 0.085	0.227	0.243	0.268	0.304	0.349	0.406	0.462	0.500	0.536	0.594
	Pregnancy 36th week	5000	0.329 ± 0.072	0.209	0.225	0.247	0.281	0.323	0.372	0.422	0.453	0.482	0.517
	Postpartum 6th week	5000	0.342 ± 0.062	0.257	0.272	0.292	0.327	0.369	0.418	0.469	0.499	0.521	0.544
	Postpartum 27th week	5000	0.352 ± 0.067	0.265	0.279	0.298	0.334	0.380	0.433	0.490	0.527	0.555	0.580
23 to < 30	Non-pregnant females	<u>54</u>	0.221 ± 0.035	0.153	0.164	0.176	0.197	0.221	0.244	0.265	0.278	0.289	0.301
	Prepregnancy 0 week	5000	0.222 ± 0.035	0.167	0.174	0.181	0.199	0.218	0.242	0.269	0.285	0.302	0.317
	Pregnancy 9th week	5000	0.308 ± 0.189	0.224	0.233	0.243	0.269	0.298	0.333	0.371	0.395	0.420	0.458
	Pregnancy 22nd week	5000	0.321 ± 0.067	0.230	0.239	0.252	0.277	0.310	0.351	0.399	0.433	0.467	0.521
	Pregnancy 36th week	5000	0.297 ± 0.056	0.212	0.220	0.233	0.258	0.289	0.328	0.369	0.399	0.421	0.448
	Postpartum 6th week	5000	0.309 ± 0.045	0.255	0.265	0.278	0.302	0.333	0.368	0.402	0.425	0.445	0.464
	Postpartum 27th week	5000	0.317 ± 0.049	0.259	0.269	0.283	0.309	0.342	0.380	0.416	0.441	0.464	0.490
30 to 55	Non-pregnant females	<u>61</u>	0.229 ± 0.035	0.160	0.171	0.184	0.206	0.229	0.253	0.274	0.287	0.298	0.311
	Prepregnancy 0 week	5000	0.229 ± 0.035	0.169	0.174	0.187	0.202	0.229	0.253	0.275	0.287	0.297	0.302
	Pregnancy 9th week	5000	0.314 ± 0.069	0.227	0.237	0.252	0.276	0.309	0.346	0.382	0.400	0.415	0.443
	Pregnancy 22nd week	5000	0.330 ± 0.069	0.231	0.242	0.257	0.285	0.321	0.365	0.409	0.439	0.478	0.522
	Pregnancy 36th week	5000	0.303 ± 0.057	0.216	0.225	0.238	0.264	0.297	0.336	0.373	0.401	0.429	0.461
	Postpartum 6th week	5000	0.316 ± 0.046	0.257	0.267	0.280	0.307	0.343	0.382	0.416	0.434	0.449	0.467
	Postpartum 27th week	5000	0.325 ± 0.050	0.261	0.272	0.285	0.314	0.352	0.394	0.432	0.453	0.471	0.491

[a]Normal-weight females are defined as those having a body mass index varying between 19.8 and 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $\underline{n}_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Resulting TDERs from the integration of energetic and weight measurements in normal-weight non-pregnant and non-lactating females (IOM, 2002; n=172) with those during pregnancy (Butte *et al*. 2004; n=34) and lactation (Goldberg *et al*. 1991, n= 10; IOM 2002, n=28) by Monte Carlo simulations (Table Web-12) were converted into physiological daily inhalation rates by the following equation: TDER*H*(V_E/VO_2)*10^{-3}. TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure. The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine or saliva samples were monitored by gaz-isotope-ratio mass spectrometry for a 7 to 21-day period per subject. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 for non-pregnant, non-lactating and prepregant females (Layton 1993). During pregnancy V_E/VO_2 = 36.8 at the 9th and 22nd week and 36.2 at the 36th week. During postpartum, V_E/VO_2 = 34.5 and 34.2 for breastfeeding mothers at the 6th and 27th week postpartum postpartum respectively (Pernoll *et al.* 1975).

Tables Web-1 and Web-12 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Table 21 Distribution of physiological daily inhalation rate (m^3/kg-day) percentiles for free-living overweight/obese[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle		Number of subjects [b] <u>n</u> $_{E xp.}$ or n $_{Sim.}$	Physiological daily inhalation rates[c] (m^3/kg-day) Mean ± S.D.	Percentile									
					2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
11 to < 23	Non-pregnant females		<u>15</u>	0.206 ± 0.033	0.141	0.151	0.163	0.184	0.206	0.229	0.249	0.261	0.272	0.284
	Prepregnancy	0 week	5000	0.207 ± 0.032	0.144	0.146	0.153	0.188	0.214	0.227	0.240	0.253	0.258	0.259
	Pregnancy	9[th] week	5000	0.302 ± 0.075	0.196	0.205	0.223	0.263	0.298	0.329	0.368	0.401	0.441	0.515
	Pregnancy	22[nd] week	5000	0.287 ± 0.079	0.184	0.191	0.206	0.246	0.279	0.314	0.357	0.391	0.436	0.512
	Pregnancy	36[th] week	5000	0.270 ± 0.090	0.169	0.179	0.193	0.225	0.259	0.296	0.337	0.377	0.429	0.521
	Postpartum	6[th] week	5000	0.280 ± 0.050	0.202	0.213	0.230	0.266	0.301	0.337	0.372	0.395	0.419	0.444
	Postpartum	27[th] week	5000	0.285 ± 0.053	0.204	0.214	0.233	0.269	0.307	0.344	0.381	0.409	0.434	0.464
23 to < 30	Non-pregnant females		<u>25</u>	0.186 ± 0.025	0.136	0.144	0.153	0.169	0.186	0.203	0.218	0.227	0.235	0.244
	Prepregnancy	0 week	5000	0.186 ± 0.025	0.138	0.143	0.155	0.172	0.183	0.201	0.222	0.233	0.235	0.236
	Pregnancy	9[th] week	5000	0.274 ± 0.068	0.195	0.203	0.217	0.238	0.263	0.298	0.337	0.374	0.421	0.476
	Pregnancy	22[nd] week	5000	0.261 ± 0.069	0.184	0.193	0.205	0.224	0.248	0.283	0.323	0.360	0.403	0.466
	Pregnancy	36[th] week	5000	0.245 ± 0.074	0.166	0.175	0.185	0.205	0.231	0.268	0.314	0.360	0.415	0.498
	Postpartum	6[th] week	5000	0.256 ± 0.042	0.197	0.205	0.217	0.241	0.271	0.304	0.338	0.360	0.381	0.406
	Postpartum	27[th] week	5000	0.260 ± 0.046	0.200	0.209	0.222	0.246	0.277	0.311	0.349	0.372	0.398	0.426
30 to 55	Non-pregnant females		<u>64</u>	0.184 ± 0.031	0.122	0.132	0.144	0.163	0.184	0.205	0.224	0.235	0.245	0.257
	Prepregnancy	0 week	5000	0.184 ± 0.031	0.118	0.127	0.141	0.166	0.185	0.205	0.221	0.226	0.235	0.246
	Pregnancy	9[th] week	5000	0.272 ± 0.068	0.172	0.184	0.203	0.234	0.263	0.299	0.343	0.378	0.416	0.465
	Pregnancy	22[nd] week	5000	0.259 ± 0.071	0.164	0.176	0.194	0.222	0.249	0.282	0.322	0.363	0.415	0.490
	Pregnancy	36[th] week	5000	0.242 ± 0.068	0.150	0.162	0.177	0.201	0.230	0.265	0.313	0.351	0.393	0.455
	Postpartum	6[th] week	5000	0.253 ± 0.048	0.177	0.188	0.205	0.237	0.270	0.305	0.340	0.364	0.385	0.404
	Postpartum	27[th] week	5000	0.257 ± 0.051	0.179	0.191	0.208	0.239	0.273	0.310	0.348	0.374	0.399	0.430

[a]Overweight/obese females are defined as those having a body mass index higher than 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] <u>n</u>$_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Resulting TDERs from the integration of energetic and weight measurements in overweight/obese non-pregnant and non-lactating females (IOM, 2002; n=104) with those during pregnancy (Butte *et al*. 2004; n=12) and lactation (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by Monte Carlo simulations (Table Web-13) were converted into physiological daily inhalation rates by the following equation: TDER*H*(V_E/VO_2)*$10^{-3.}$ TDER = total energy requirement (ECG + TDEE). ECG = stored daily energy cost for growth; TDEE = total daily energy expenditure. The ECG and TDEE were based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine or saliva samples were monitored by gaz-isotope-ratio mass spectrometry for a 7 to 21-day period per subject. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 for non-pregnant, non-lactating and prepregant females (Layton 1993). During pregnancy V_E/VO_2 = 36.8 at the 9[th] and 22[nd] week and 36.2 at the 36[th] week. During postpartum, V_E/VO_2 = 34.5 and 34.2 for breastfeeding mothers at the 6[th] and 27[th] week postpartum postpartum respectively (Pernoll *et al.* 1975).

Tables Web-1 and Web-13 are available on the Québec Ministry of Sustainable Development, Environment and Parks Web site (MDDEP 2006).

Avant-propos en rapport aux figures synthèses des Articles I et II

Les Articles I (Brochu *et al.* 200a), II (Brochu *et al.* (2006b) et Brochu *et al.* (2006c) ont été publiés dans la revue « *Human and Ecological Risk Assessment* ». Compte tenu des nombreux tableaux (55) et figures (10) spécifiques à ces publications, il a été convenu avec l'étiteur, de présenter certains tableaux (30) et toutes les figures sur le site Internet du Ministère du développement durable, de l'environnement et des parcs (MDDEP), du Gouvernement du Québec. Les adresses suivantes de ce site Web sont spécifiées à la page 53 de l'Article I et à la page 114 de l'Article II de la thèse :

http://www.mddep.gouv.qc.ca/air/inhalation/index.htm (information en français) ;
http://www.mddep.gouv.qc.ca/air/inhalation/index_en.htm (information en anglais).

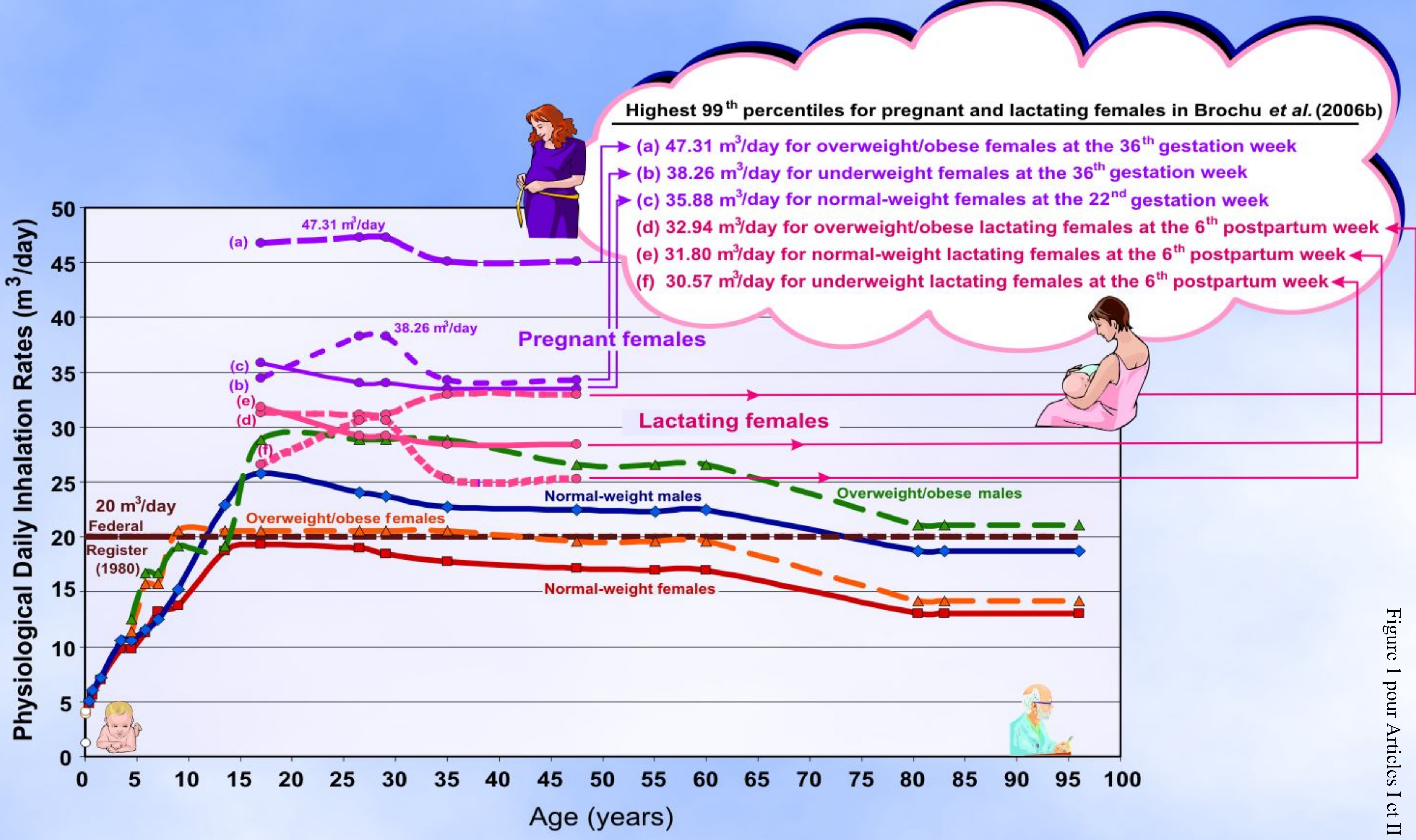
Vous trouverez aux pages suivantes les Figures synthèses 1 et 2 du site Web du MDDEP des 99^{e} centiles des taux physiologiques quotidiens d'inhalation des Articles I et II (en m^3/jour, puis en m^3/kg-jour) en fonction de l'âge des sujets.

99th Percentiles of Physiological Daily Inhalation Rates (m^3/day) as a Function of Age for Individuals Aged 3 Weeks to 96 Years

(reflect the total daily oxygenation requirements in free-living people for an aggregate period of over 36,000 days for 2567 individuals)

International Journal of Human and Ecological Risk Assessment, HERA. 12(4), August 2006 (Brochu *et al*. 2006a, 2006b).

Pierre Brochu[1,2], Jean-François Ducré-Robitaille[1] and Jules Brodeur[2]



[1] Affiliated to the Ministry of Sustainable Development, Environment and Parks.
[2] Affiliated to the Faculty of Medicine of the University of Montréal.

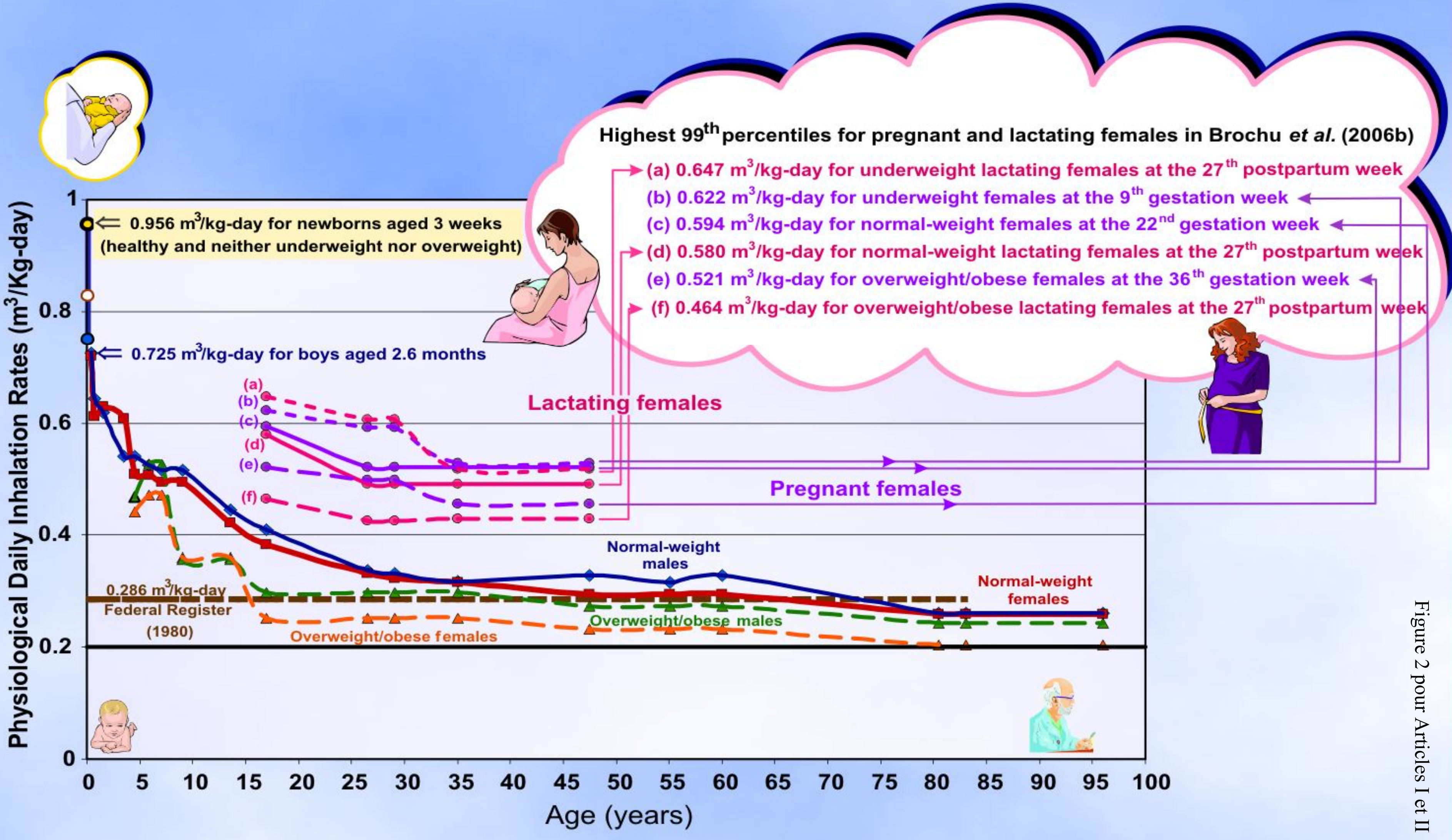
Graphic design, Francine Matte B. es Art

99th Percentiles of Physiological Daily Inhalation Rates (m^3/kg-day) as a Function of Age for Individuals Aged 3 Weeks to 96 Years

(reflect the total daily oxygenation requirements in free-living people for an aggregate period of over 36,000 days for 2567 individuals)

International Journal of Human and Ecological Risk Assessment, HERA 12(4), August 2006 (Brochu *et al*. 2006a, 2006b).

Pierre Brochu[1,2], Jean-François Ducré-Robitaille[1] and Jules Brodeur[2]



[1] Affiliated to the Ministry of Sustainable Development, Environment and Parks.
[2] Affiliated to the Faculty of Medicine of the University of Montréal.

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4 Article III

Derivation of physiological inhalation rates in children, adults and elderly based on nighttime and daytime respiratory parameters

DERIVATION OF PHYSIOLOGICAL INHALATION RATES IN CHILDREN, ADULTS AND ELDERLY BASED ON NIGHTTIME AND DAYTIME RESPIRATORY PARAMETERS

Pierre Brochu[1, 2, 3], Jules Brodeur[2] and Kannan Krishnan[2]

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[1] Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi et de l'état de l'environnement, Service des avis et expertises scientifiques, gouvernement du Québec, édifice Marie-Guyart, 7[e] étage, 675, boulevard René-Lévesque Est, Québec, QC, G1R 5V7, Canada.

[2] Département de santé environnementale et santé au travail, Faculté de médecine, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, QC, H3C 3J7, Canada.

[3] To whom all correspondence should be addressed.

ABSTRACT

Based on an exhaustive compilation and a critical analysis of a wide range of published data related to the oxygen uptake factors and ventilatory equivalents, nighttime and daytime respiratory parameters were determined and integrated into the calculation process of physiological daily inhalation rates in normal-weight males and females aged 0.22 to 96 years. The oxygen uptake factors during fasting (0.2057 ± 0.0018 L of O_2/kcal; mean ± S.D.) and postprandial phases (0.2059 ± 0.0019 L of O_2/kcal) as well as ventilatory equivalents for subjects at rest (27.4 ± 4.8 to 32.2 ± 3.1) and during the aggregate daytime activities (29.9 ± 4.2 to 33.7 ± 7.2), were combined for calculations with published basal and total energy expenditures. These energetic values were resulting from indirect calorimetry measurements (n=1235) and disappearance rates of oral doses of deuterium (^2H) and heavy oxygen-18 (^{18}O) in urine for an aggregate period of over 19, 000 days respectively. The highest 99th percentiles for daily inhalation values were found in males aged 35 to less than 45 years (35.40 m^3/day), 2.6 to less than 6 months (1.138 m^3/kg-day) and 10 to less than 16.5 years (22.29 m^3/m^2-day). Mean and percentile inhalation values expressed in m^3/kg-day as well as m^3/m^2-day suggest generally higher intakes of air pollutants in children than adults, and males than females (in µg/kg-day and µg/m^2-day respectively) during identical exposure concentrations and conditions. For instance, mean physiological daily inhalation rates in boys aged 2.6 to less than 6 months of 10.99± 3.50 m^3/m^2-day and 0.572 ± 0.191 m^3/kg-day are 1.3 and 2.5 fold higher respectively than those in adult males 65 to 96 years old (8.42 ± 2.13 m^3/m^2-day, 0.225 ± 0.059 m^3/kg-day).

Key words: daily inhalation rates, oxygen uptake factor, ventilatory equivalent, doubly labeled water, risk assessment.

LIST OF MAIN ABBREVIATIONS

α: data for the aggregate daytime activities of subjects

β: data for subjects under resting conditions

BEE: basal energy expenditure (BMR expressed on a 24-hour basis)

BMI: body mass index

BMR: basal metabolic rate (punctual measurement)

BSA: body surface area

BTPS: body temperature pressure saturation

DLW: doubly labeled water

E: minute energy expenditure rate

ECG: stored daily energy cost for growth

H: oxygen uptake factor, volume of oxygen (at STPD) consumed to produce 1 kcal of energy expended

RER: VCO_2/VO_2 ratio, more properly known as the respiratory exchange ratio

Sld: sleep duration

SMR: sleeping metabolic rate

STPD: standard temperature and pressure, dry air

TDEE: total daily energy expenditure

VCO_2: carbon dioxide production rate

VE: minute ventilation rate

VO_2: oxygen consumption rate (also known as the oxygen uptake)

VQ: ventilatory equivalent for VO_2 (VE at BTPS /VO_2 at STPD)

INTRODUCTION

Accurate values for daily inhalation rates in humans are required for health risk assessment and management of air pollutants (Health Canada 1996; van Engelen and Prud'homme de Lodder 2007) especially for the young and aged, known as being more susceptible than adults to the adverse health effects of airborne chemicals (Braun-Fahrländer *et al.* 1997; Tolbert *et al.* 2000; Liu *et al.* 2003; Yang *et al.* 2003).

Estimates of daily inhalation rates in humans have been greatly improved with the use of the energy expenditure approach of Layton (1993). This approach has been formulated in a basic equation comprising the following terms: E (mean energy expenditure required for a given activity level expressed as kcal/min), H (oxygen uptake factor expressed as L of oxygen consumed/kcal expended) and VQ (ventilatory equivalent ratio of the minute ventilation rate to the oxygen consumption rate, unitless). Nevertheless, the procedures developed by Layton (1993) to estimate E values are not free from biases and were showed to generate errors of daily inhalation estimates ranging from -36 to +60% (Brochu *et al.* 2006c). The difficulty in achieving accurate estimations of E values has been addressed by Brochu *et al*. (2006a, 2006b) with the use of total daily energy expenditures (TDEE) that are measured from the doubly labeled water (DLW) method (Bluck 2008). Values for TDEE systematically encompass voluntary and involuntary energy expended by humans during real-life situations in their normal surroundings each minute of the day, 24-hours per day, on a daily basis for 7 to 21 days (IDECG 1990).

The precise value of the two other parameters in the equation of Layton (i.e. H and VQ) is still a matter for discussion. A postprandial H value of 0.21 L of O_2/kcal has been first calculated for Americans by Layton (1993) and later confirmed for Canadians by Brochu *et al* (2006a). However, a critical analysis of possible fluctuations in the postprandial H value as a function of age, sex, and typical dietary intakes in various countries has not been performed. Moreover, the variation of H values during nighttime sleep in fasting subjects has never been taken into account in the calculation process of daily inhalation rates. Similarly, VQ values have been shown to vary from 34.2 to 36.8 in pregnant and lactating women in Brochu *et al.* (2006b) compared with the constant value of 27 reported in Layton (1993). However, the accurate variation of VQ values in non gestational and lactating individuals as a function of age has not yet been reliably characterized.

The present paper is therefore intended to improve the methodology developed previously by Brochu *et al*. (2006a, 2006b, 2006c) for a scientifically-sound determination of daily inhalation rates in free-living individuals based on DLW measurements. The overall approach involved the determination and integration of the means and standard deviations values for E, H and VQ for nighttime sleep (fasting phase) and daytime activities (postprandial phase) into the calculation process of physiological daily inhalation rates in normal-weight individuals.

METHODOLOGY

Study Design

Means and standard deviations (S.D.) for H and VQ were determined initially and then used subsequently in the second part, with those of E and sleep durations, for the calculation of the physiological daily inhalation rates. Data for athletes and explorers were excluded from the calculation process of the latter values. Daily inhalation values were expressed as absolute values (m^3/day), as well as relative values to the body-weight (m^3/kg-day) and body surface area (m^3/kg-m^2). Normal-weight individuals were defined according to the following body mass index (BMI) cut-offs: from the 3rd to 97th percentiles for children under 3 years old, the 85th percentile or below for children aged 3 to 19 years, and from 18.5 to 24.5 kg/m^2 for adults over 19 up to 96 years (IOM 2002). Infants, toddlers, children and teenagers are hereafter referred to collectively as children.

Values for E were determined by using individual DLW measurements taken from the database reported in IOM (2002) for healthy normal-weight males and females aged 2.6 to 96 years (n=1235). These values, which are systematically measured with the DLW method, include subject-specific information on body weight, height, BMI value, basal energy expenditure (BEE) and TDEE values. Values for BEE were measured by indirect calorimetry (Ferrannini 1988; Bursztein *et al.* 1989), while those for TDEE were obtained by mass spectrometric monitoring of disappearance rates of oral doses of water isotopes usually monitored in the urine (IDECG 1990). Values for E during nighttime sleep were calculated by using BEE values. Those during the aggregate daytime activities are the result of subtracting BEE from TDEE values. The basic principles of indirect calorimetry and the DLW method are summarised in Brochu *et al.* (2010b).

An exhaustive compilation and a critical analysis of published data in healthy subjects were performed in order to select appropriate parameters for the determination of H values during postprandial and fasting phases (i.e. typical diets found in various countries, respiratory gas-exchange measurements of oxygen and carbon dioxide) and VQ values under resting conditions and for the aggregate daytime activities (i.e. simultaneous measurements of minute ventilation and oxygen consumption rates) (Appendix I).

Food recall surveys (i.e. retrospective method) or weighed dietary records (i.e. prospective method using household measures or collection of duplicate diets) are used to describe dietary intakes in subjects (Torun *et al.* 1996). Experimental procedures used for measurements of oxygen consumption rate (VO_2), carbon dioxide production (VCO_2) and minute ventilation rate (VE) are specified in each publication. However, VO_2 and VCO_2 values are often measured using paramagnetic O_2 and infrared CO_2 analysers respectively (Skoog *et al.* 2006). Values for VE are generally measured by spirometry and sometime by pneumotacography (Mason *et al.* 2005). Sleep durations are recorded day-by-day on questionnaires by survey respondents for extensive periods of time (usually longer than a year) including complementary data, as those regarding work conditions, physical activities, diets, as well as health and socioeconomic variables (*e.g.* Bjorvatn *et al.* 2007).

$VO_2\beta$ and $VO_2\alpha$: criteria for data selection for H and VQ calculations

Published sets of measurements for VE, VO_2 and VCO_2, VO_2 values measured in healthy subjects at rest or performing various activities at about the sea level, when breathing an oxygen concentration of 21%, were ranked per age groups. Then, only those measured in subjects with experimental VO_2 demands within the span of typical VO_2 values for resting conditions (referred to as β) or the aggregate daytime activities (referred to as α) were included in the present study. Values for $VO_2\beta$ and $VO_2\alpha$ were preliminary calculated by using BEE and TDEE values reported in the database of the IOM (2002) for healthy normal-weight individuals (age = 2.6 months - 96 years; n = 1235). According to Layton (1993), VE (L/min) is expressed as a function of H (L of O_2/kcal), E (kcal/min) and VQ (i.e. VE/VO_2 ratio, unitless) values as follows:

$$VE = E \times H \times VQ \tag{1}$$

Hence,

$$VO_2 = E \times H \tag{2}$$

where, H is the volume of oxygen consumed at standard temperature and pressure, dry air (STPD) to produce 1 kcal of energy expended, while VQ is the ratio of the VE value at body temperature and saturated with water vapour (BTPS) to the VO_2 value at STPD.

Therefore, values for minute energy expenditure rates ($E\beta$ and $E\alpha$ in kcal/min) as well as $VO_2\beta$ and $VO_2\alpha$ (L/min) were expressed in terms of BEE and TDEE values (kcal/day) as well as the daily energy costs for growth (ECG, in kcal/day) and sleep durations (Sld, in hour/day) by using the following equations:

$$E\beta = \left[\frac{BEE + ECG}{1440}\right] \tag{3}$$

$$E\alpha = \left[\frac{TDEE - BEE}{(24 - Sld) \times 60}\right] + \left[\frac{BEE + ECG}{1440}\right] \tag{4}$$

$$VO_2\beta = \left[\frac{BEE + ECG}{1440}\right] \times H \tag{5}$$

$$VO_2\alpha = \left[\frac{(TDEE - BEE)}{(24 - Sld) \times 60} + \frac{(BEE + ECG)}{1440}\right] \times H \tag{6}$$

where 1440 and 60 are the conversion factors from days to minutes and hours to minutes respectively and 24 is the number of hours in a day.

Values for ECG were added to BEE values in order to take into account the energy demands required during the growth process from birth up to 18 years of age for females and 24 years old for males (Brochu *et al.* 2006a). The BEE value corresponds to the basal metabolic rate (BMR) expressed during a 24-hour period. The BMR value is defined as the sum of the total energy expenditure required to maintain the minimal tissue cellular activity in order to sustain vital functions, notably blood circulation, respiration, gastrointestinal and renal processes (Guyton, 1991). BMR values are measured under standard conditions in a comfortably warm room, with subject lying at complete rest in thermoneutral conditions and having fasted for 12 to 13 hours. Respiratory gas-exchange rates are measured for subjects 40 minutes immediately after waking (e.g. Butte *et al.* 2004). The postprandial H value of 0.21 L of O_2/kcal used by Layton (1993) and Brochu *et al*. (2006a, 2006b, 2006c) is in accordance with that calculated in the present study (0.207 L of O_2/kcal) by using VO_2 and BMR values per unit of organ weight established by Malcom and Hollyday (1971). Values for VO_2 per unit of tissue weight (3.7 to 123.8 L of O_2/kg-day) for brain, liver, heart, kidneys and muscles reported in Malcom and Hollyday (1971) for adults correspond to a mean H value of 0.207 L of O_2/kcal for these five organs when divided by their respective basal metabolic rates (17.6 to 606 kcal/kg of organ per day). Consequently, a H value of 0.21 L of O_2/kcal was used for the calculation of the lower and upper limits of $VO_2\beta$ and $VO_2\alpha$ for the different age groups in this study (Tables 1 and 2).

H values

Variations of the postprandial H value (referred to as H_P value) as a function of age, sex and country were calculated based on typical dietary intake contributions found in seventeen countries. This is done by taking into account absorption rates of ingested protein, fat and carbohydrates (92, 95 and 98% respectively) through the gastrointestinal tract (Guyton, 1991) and considering that the oxidation of one gram each of these nutrients consumes 0.97, 0.83 and 2.0 L of O_2 and yields 4.5, 9.5 and 4.2 kcal of energy respectively (McLean and Tobin 1987; Layton 1993; Brochu *et al.* 2006a). Values for H_P and H for fasting subjects (referred to as H_F value) were also calculated by using values for VO_2 and VCO_2, or alternatively using VO_2 and respiratory exchange ratios (i.e. VCO_2/VO_2, known as the RER value) simultaneously measured by indirect calorimetry at STPD in the same subjects. Then, values for VO_2 and VCO_2 (L/min) were converted into minute energy expenditure rate (E, kcal/min) and H (L/kcal) by using the following equations (Weir 1949):

$$E = 3.941 \times VO_2 + 1.106 \times VCO_2 \qquad (7)$$

$$H = VO_2 \times (3.941 \times VO_2 + 1.106 \times VCO_2)^{-1} \qquad (8)$$

The combustion of carbohydrates, protein and fat from ingested food requires 0.199, 0.212 and 0.221 L of O_2 per kcal of energy expended respectively (McLean and Tobin 1987). During the fasting phase, 0.198, 0.200, 0.210, 0.211 and 0.214 L of O_2/kcal are required for the combustion of glycogen, glucose, 3-hydroxybutyric acid, acetoacetic acid and triacylglycerol respectively (Elia 1997). Consequently, a minimum of 0.199 L of O_2/kcal and maximum of 0.221 L of O_2/kcal for H_P values (McLean and Tobin 1987), as well as minimal and maximal H_F values of 0.198 and 0.214 L of O_2/kcal respectively (Elia 1997) were used into the calculation process of physiological daily inhalation rates.

VQ values

Values for VQ were calculated by dividing VE by VO_2 values simultaneously measured for the same subjects at BTPS and STPD respectively. Voluntary and involuntary activities during daytime are performed by individuals in the sitting or standing position. Therefore, VQα values were calculated exclusively by using published VEα and $VO_2α$ measured while subjects were in the upright position. The data for subjects in the supine position were insufficient to calculated VQβ values. However, only slightly higher energy expenditure is required when subjects, during resting conditions, change from a supine to an upright position, which consequently increase VO_2, VCO_2, VE values by about the same extent (e.g. Donevan *et al.* 1962; Damato *et al.* 1966). Conversely, lower BMR values observed in normal-weight subjects during profound sleep (e.g. Ravussin *et al.* 1985; Garby *et al.* 1987) slightly reduce VE and VO_2 demands as well (e.g. Colrain *et al.* 1987). These fluctuations of VO_2 demands combined with the change of VE and VO_2 values always remain within the span of $VO_2β$. Therefore, VQβ values were calculated by using sets of VEβ and $VO_2β$ values measured in subjects in the upright position. Such VQβ values can be used to characterize VQ values for subjects during resting conditions in the upright or supine position as well as during nighttime sleep.

Published sets of VE and VO_2 values were found for individuals aged less than 1 year and for those from 4 to 91 years in the supine and upright positions respectively. No data was available for children from 1 to less than 4 years of age. Thus, VQ values for the latter aged group were assumed to be the same as those for children aged 1 to less than 10 years. Mean $VQ\beta$ values of 30.2±7.6 and 30.8 ± 0.9 calculated for non sedated children aged 2 hours to 1.4 months (Cook *et al.* 1955; Stahlman and Meece 1957; Nelson *et al.* 1962; n=131) and 4 to less than 10 years respectively (Robinson 1938; Inbar *et al.* 1981; n=35) are within the same order of magnitude, and both appear to be slightly higher than the value of 27.0 ± 4.3 based on data reported in Lees *et al.* (1967) for sedated children aged 0.5 to 8.5 months (n=26). Therefore, the former value (i.e. 30.2±7.6) was used to characterize $VQ\beta$ in children aged 2.6 months to less than 1 year rather than the latter (i.e. 27.0 ± 4.3). The $VQ\alpha$ value for children aged less than 1 year-old was assumed to be the same as the $VQ\beta$ value since such children have limited physical capacity and opportunities for doing a great deal of demanding exercises (Polgar and Weng, 1979; Guyton, 1991). No published VE and VO_2 were found for children from 1 to less than 10 years of age for VO_2 demands within the span of $VO_2\alpha$. Values for $VQ\beta$ and $VQ\alpha$ for the latter age group were assumed to be the same (i.e. 30.8 ± 0.9), considering the small difference found between $VQ\beta$ (27.7 ± 3.4, n=145) and $VQ\alpha$ (29.9 ± 4.2, n=166) values in older children aged 10 to less than 16.5 years (Table 8).

Accuracy of energetic measurements

The accuracy of E, as well as the BEE values based on the gas exchange of VO_2 and VCO_2 monitored by indirect calorimetry and calculated with the use of the Weir equation (equation 7) has been shown to vary from +1 to +2% compared to values measured by steady state direct calorimetry in a sealed chamber (Turel and Alexander 1964). Consequently, H_P and H_F values calculated based on the equation 8 are affected by an error ranging from -2 to -1%. During DLW measurements, subjects are advised not to change their usual sources of ingested water for the entire duration of the study. Changing water sources during the isotope elimination period has been found to lead to an increase in the mean error of TDEE values by -8.7% in infants and +5.3% in soldiers (Delany *et al.* 1988; Jones *et al.* 1988). However, the mean accuracy of TDEE values from DLW method have been validated against other methods, including metabolic chambers as varying from -1.0 to +3.3% when the sources of tap water were not modified during the entire period (IDECG 1990). This range of errors also affects the accuracy of ECG values (Brochu *et al.* 2006a). Therefore, the combined effects of simultaneous minimal and maximal mean errors associated with H_P, H_F (i.e. -2 to -1%), BEE (i.e. +1 to +2%), TDEE and ECG values (i.e. -1.0 to +3.3%) on the order of magnitude of physiological daily inhalation rates were determined in the present study.

Physiological daily inhalation rates

Tidal volumes, breathing frequency rates, VE and VO_2 values (e.g. Tabachnik *et al.* 1981; Colrain *et al.* 1987; Hudgel *et al.* 1993; Morrell *et al.* 1995), systolic and diastolic blood pressures and heart rates have all been shown to be lower in sleeping subjects compared with their awaken counterparts (e.g. Carrington *et al.* 2005; Zaregarizi et al. 2007). These findings are in accordance with the reduction of BMR values during sleep. Based on heat production measured in sleeping subjects by direct calorimetry, the sleeping metabolic rates (SMR) were calculated to be 0.960 ± 0.023 times the BMR values in normal-weight (n=86) individuals (Benedict and Carpenter 1910; Buskirk *et al*. 1960; Bessard *et al.*

1983; Schutz *et al.* 1984; Shapiro *et al.* 1984; Ravussin *et al.* 1985; Garby *et al.* 1987). This correcting factor (referred to as Fsleep) affecting BEE values as well as the minimal and maximal Fsleep values of 0.870 and 1.039 were integrated into the following equation in order to determine the SMR values (in kcal/min) for subjects during sleep in the supine position:

$$SMR = \left[\frac{(BEE \times Fsleep) + ECG}{1440}\right] \tag{9}$$

Values for physiological daily inhalation rates (m^3/day) were then calculated by using the following expression:

$$PDIR = \left[(SMR \times H_F \times VQ\beta \times Sld) + (E\alpha \times H_P \times VQ\alpha) \times (24 - Sld)\right] \times 0.06 \tag{10}$$

where 0.060 is the combined conversion factor from hours to minutes and litres (L) to cubic meters (m^3).

Values for physiological daily inhalation rates expressed per unit of body surface area (BSA) were determined by using the BSA values calculated on the basis of height (cm) and weight (kg) values as follows (Mosteller 1987):

$$BSA = \left[\frac{height \times weight}{3600}\right]^{0.5} \tag{11}$$

Sleep durations

Sleep durations from the literature were used in this study regardless of the under-, normal-weight, overweight and obese proportions of individuals in the different cohorts.

However, several publications suggest that overweight and obese children and adults have shorter night sleep compared to their normal-weight counterparts (Taheri *et al.* 2004; Cizza *et al.* 2005; Gangwisch *et al.* 2005; Vorona *et al.* 2005; Beebe *et al.* 2006; Kohatsu *et al.* 2006; Patel *et al.* 2006; Taheri 2006; Bjorvatn *et al.* 2007; Seicean *et al*. 2007). On the contrary, some publications challenge this view (Koçoglu *et al.* 2003; Gibson *et al.* 2004; Hasler *et al.* 2004; Eisenmann *et al*. 2006). To dispel the influence of this ambiguity on inhalation values, two sets of daily inhalation rates were calculated and compared.

A first set of physiological daily inhalation rates was calculated by using the sleep durations reported in Bernstein *et al.* (2001) and Eisenmann *et al.* (2006) for small cohorts of subjects composed of known proportions of normal-weight, overweight and obese individuals (i.e. 10.9% of boys and 13.6% of girls aged 7.5 to 10.9 years, 10.7% of males and 11.9% of females aged 11 to 16.5 years were overweight or obese; in adults aged 35 to 74 years, 45% of males and 24% of females were overweight, 9% of males and 13% of females were obese). This set of values was compared to a second set of inhalation rates that was calculated when sleep durations for percentages of overweight/obese individuals in both cohorts were decreased by 25%. This process of calculation corresponds to the worst case scenario based on data reported in the literature. Sleep durations for 60% of overweight/obese children were decreased by 25% based on published values that indicate that 13.5 to 57.6% of overweight/obese children aged 7.5 to 16.5 years (n=6426) have sleep deprivation varying from 13.1 to 21.9% (Eisenmann *et al.* 2006; Seicean *et al*. 2007). Sleep durations for 35% of overweight adults and 55% of their obese counterparts were decreased by 25% considering the fact that 27.8 to 35.1% of overweight adults and 29.3 to 53.1% of their obese counterparts (n=96,570) aged 32 to 86 years (Gangwisch *et* *al*. 2005; Kohatsu *et al.* 2006; Patel *et al.* 2006; Bjorvatn *et al*. 2007) have sleep durations 14.3 to 25.4% and 16.4 to 26.2% respectively shorter than the healthy baseline of 7 hours per night (Kripke *et al.* 2002; Patel *et al.* 2004; Cizza *et al*. 2005; Gangwisch *et al*. 2005; Seicean *et al.* 2007).

Statistical analysis

Means, S.D. values and distribution percentiles were calculated for all values, which were grouped by age with more than 30 subjects per group in order to optimize the probability of achieving a normal distribution for each age group, as formally recommended according to the central limit theorem (Feller 1945; Trotter 1959; Rice 1995). Monte Carlo simulations were used in order to take into account S.D. values into mean calculations and different physiological equations. Each calculation process was based on random sampling involving 10,000 iterations. Lognormal distributions of sleep durations were used into the calculation process of physiological daily inhalation rates based on data reported in Knutson and Lauderdale (2007) and Seicean *et al*. (2007). Distributions of other parameters were defined to be either lognormal or normal according the Anderson-Darling goodness-of-fit tests performed on individual data (Tables 1, 2, 7 and 8). The same statistical test was used to define the best fit distributions of the resulting physiological daily inhalation rates per age group. The number of individual observations in fasting subjects reported in Gibney *et al*. (2003) and Shepherd *et al.* (2007) was insufficient (n=8) for the use of the Anderson-Darling test. Therefore, individual H_P (n=102) values for subjects in the supine position were statically tested in order to characterize the distribution type for the H_F value during nighttime sleep.

RESULTS

Mean and S.D. values for body weights, BSA, BEE, ECG and TDEE as well as lower and upper limits of $VO_2\beta$ and $VO_2\alpha$ are presented in Tables 1 and 2, while those for sleep durations are reported in Table 3. Mean H_P values resulting from nutrient intakes in different countries are given in Tables 4 to 6. Those for Mean and S.D. values and distribution percentiles of VQβ and VQα values as well as mean and S.D. values for VQ ratios below the anaerobic threshold and during anaerobiosis are presented in Tables 8. Means and distribution percentiles of physiological daily inhalation rates in normal-weight males and females aged 2.6 months to 96 years are given in Tables 9 and 10 respectively. Mean values for daily inhalation rates as a function of age are presented in Figures 1 to 3.

Results of Anderson-Darling goodness-of-fit tests on anthropometric and energetic values are reported in Tables 1 and 2, while those on respiratory parameters are given in Table 7. Finally, physiological daily inhalation rates for all age groups in m^3/day, m^3/kg-day as well as m^3/m^2-day better fit with lognormal distributions except for those in m^3/day for girls aged 1 to less than 2 years which better fit with a normal distribution (not presented in Tables).

Values for H_P based on dietary intakes were found to vary between 0.203 and 0.208 L of O_2/kcal in seventeen countries (Table 4), albeit North-American values range from 0.206 to 0.208 L of O_2/kcal. H_P values for the Canadian population range from 0.205 to 0.207 L of O_2/kcal for in term infants after birth and remain relatively constant (variation of values ≤0.5%) into advanced age (Table 5). Values for H_P were confirmed to almost always be identical between males and females of the same age living in the same country. Variations observed were consistently less than 0.4% (Table 6). Values of 0.206, 0.207 and 0.209 L of O_2/kcal were calculated for the 10^{th}, 50^{th}, and 90^{th} percentiles based on Canadian nutrient intake contributions observed and compiled by Brault-Dubuc and Mongeau (1989) over a 10-year span (n=747). H_P values were calculated to be 0.206, 0.207, 0.207 L of O_2/kcal for under-weight (n=14), normal-weight (n=25) and obese adults (n=18) respectively, based on typical German diet (Bosy-Westphal *et al.* 2004). H_P values for black (n=246) and white Americans (n=703), calculated in this study, based on their nutrient intakes (Morisson *et al.* 1980) vary by less then 0.5%.

Results of H_P and H_F values calculated based on simultaneous VO_2 and VCO_2 measurements are not presented in Tables. Values for an H_F of 0.205 ± 0.003, 0.206 ± 0.003 and 0.207 ± 0.003 L of O_2/kcal for subjects at rest in a semi-recumbent (Müeller *et. al* 1989; n=5), almost supine (Saltzman and Salzano 1971; n=20) and supine position (Gibney *et al.* 2003; n=6) were calculated with VO_2, E and RER values varying from 0.225 ± 0.035 to 0.307 ± 0.044 L/min, 1.09 ± 0.05 to 1.47 ± 0.07 kcal/min and 0.802 ± 0.057 to 0.858± 0.072 respectively. A mean H_F value of 0.205 ± 0.001 L of O_2/kcal was also calculated for adults aged 23 to 30 years (n=27) performing exercise in the upright position below the anaerobic threshold (De Bock *et al.* 2005; VO_2 of 2.83 ± 0.05 L/min, VCO_2 of 2.37 ± 0.05 L/min, E of 13.41 ± 0.21 kcal/min, RER of 0.838 ± 0.023 with minimal and maximal values of 0.759 and 0.928 respectively). These results show that the level of exertions in fasting subjects (thus VO_2 demands at rest or during exercise below the anaerobic threshold), and their positions (i.e. upright or supine position) during measurements had a negligible effect on their H_F values (by less than 1%). Consequently,

H_F and H_P values for nighttime sleep and the aggregate daytime activities respectively were calculated by using VO_2 and VCO_2 values measured in healthy subjects while performing activities with VO_2 demands that were within the entire span of $VO_2\beta$ and $VO_2\alpha$ values varying from 0.06 to 0.79 L/min (Tables 1 and 2) regardless of their positions during the experimental protocols. Values for H_F of 0.2057 ± 0.0018 L of O_2/kcal (n=31) and H_P of 0.2059 ± 0.0019 L of O_2/kcal (n=1245) were then calculated. The H_P value was calculated by using published data for individuals aged 2 hours to 73 years (n=327) in the supine position and 8.8 to 81 years (n=918) in the upright position (Tenney and Miller 1956; Baker *et al*. 1957; Spurr *et al.* 1957; Emirgil *et al*. 1967; Pernow and Saltin 1971; Oren *et al.* 1981; Allen *et al*. 1984; Capderou *et al.* 1997; Treuth *et al.* 1998; Gisolf *et al.* 2003; Cade *et al.* 2004; Shiou-Liang *et al*. 2005; other references are underlined in the Appendix I). During the postprandial phase, VO_2, E and RER values of 0.184 ± 0.011 L/min, 0.90 ± 0.04 kcal/min and 0.866 ± 0.074 respectively were calculated for individuals in the supine position, compared to a VO_2 of 0.291 ± 0.013 L/min, an E of 1.41 ± 0.05 kcal/min and a RER of 0.817 ± 0.050 for subjects in the upright position.

The worst case scenario of decreased sleep duration in overweight/obese subjects has reduced the global physiological daily inhalation rates of entire cohorts of subjects by only 0.03 to 0.17% (data not shown in Tables). Initial sleep durations (Sld) of 9.9 ± 1.2 (n=919), 9.2 ± 0.8 (n=2284), 7.8 ± 0.3 hours/day (n=1707) in males and 10.2 ± 1.0 (n=953), 9.3 ± 0.8 (n=2168), 8.2 ± 0.4 hours/day (n=1703) in females have been published for subjects aged 7.5 to 10.9, 11 to 16.5 and 35 to 74 years respectively (Bernstein *et al.* 2001; Eisenmann *et al.* 2006). Classified in the same order, initial Sld values of entire cohorts of subjects were decreased to 9.7 ± 1.1, 9.0 ± 0.8, 7.3 ± 0.3 hours/day for males and 10.0 ± 0.9, 9.1 ± 0.8, 7.9 ± 0.3 hours/day for females as a result of a 25% reduction in sleep durations for 60% of overweight/obese children and 35% of overweight as well as 55% of obese adults. Sleep durations specifically for overweight/obese subjects aged 7.5 to 10.9, 11 to 16.5 and 35 to 74 years were decreased to 7.4 ± 0.8, 6.9 ± 0.6, 5.8 ± 0.3 hours/day in males and 7.6 ± 0.7, 7.0 ± 0.6, 6.1 ± 0.3 hours/day in females respectively.

Lower and upper mean errors associated with H_P, H_F (i.e. -2 to -1%), BEE (i.e. +1 to +2%), TDEE and ECG values (i.e. -1.0 to +3.3%) affect physiological daily inhalation rates by -2.0 to -1.0, -0.08 to -0.01, -1.0 to +3.4 and -0.2 to +0.7% respectively. Simultaneous maximal mean errors associated with H_P, H_F values (-1%), BEE (+2%), ECG and TDEE values (+3.3%) increase daily inhalation values by +2.3%. The inverse scenario is observed with simultaneous minimal mean errors for H_P, H_F (-2%), BEE (+1%), ECG and TDEE (-1.0%) values affecting physiological daily inhalation rates by -3.0%. The use of SMR instead of BEE values (in equation 10) has reduced daily inhalation values by only 0.6 to 1.8%. The use of the lowest H value of 0.203 L of O_2/kcal for Vietnamese (n=17763) and the highest value of 0.208 L of O_2/kcal for American (n=74275) during the postprandial phase (Table 3) could have affected the physiological daily inhalation rates by only -1.2 to -0.7% and +0.5 to +0.9% respectively compared with the inhalation values calculated in this study based on H_P value of 0.2059 L of O_2/kcal.

DISCUSSION

All mean and almost all (98%) percentile values of physiological daily inhalation rates calculated in the present paper (in m^3/day, m^3/kg-day and m^3/m^2-day) are higher in males than in females, and are in accordance with Brochu *et al.* (2006a, 2006b, 2006c). As found in our previous studies, mean daily inhalation values expressed in m^3/kg-day follow a logarithmic pattern (Figure 2). Values drop rapidly with increasing age, up 16.5 to less than 25 years in females (R^2=0.94) and males (R^2=0.96). Then mean physiological daily inhalation rates continue to decrease slowly as age increases up to 65 to 96 years. Mean daily inhalation values in males (0.225 ± 0.059 m^3/kg-day) and females (0.202 ± 0.059 m^3/kg-day) aged 65 to 96 years are found to be 61 and 64% lower respectively than those for boys (0.572 ± 0.191 m^3/kg-day) and girls (0.563 ± 0.180 m^3/kg-day) 2.6 to less than 6 months old. When females and males age from 2.6 months to less than 16.5 years, body weights increase proportionally more (by 9.2 and 10.6 fold respectively) than height does (by 2.7 and 2.8 fold respectively). This results in a moderate increase of BSA values by 5.0 and 5.5 fold respectively. Beyond these ages very few changes appear for weight, height and BSA values. This explains why the mean physiological daily inhalation rates expressed in m^3/m^2-day begin to decrease linearly only as age increases from the age groups of 10 to less than 16.5 years for males (R^2=0.92) and 16.5 to less than 25 years for females (R^2=0.94) up to the age group of 65 to 96 years (Figure 3). Mean daily inhalation rates for boys 0.22 to less than 16.5 years old (10.99 ± 3.50 to 11.82 ± 3.50 m^3/m^2-day) and girls 0.22 to less than 10 years of age (10.81 ± 3.29 to 10.83 ± 1.84 m^3/m^2-day) are higher than those for older males and females (8.42 ± 2.13 to 10.93 ± 2.80 and 7.20 ± 1.99 to 9.90 ± 2.50 m^3/m^2-day respectively). Furthermore, in agreement with our previous study, mean physiological daily inhalation rates in females as well as males aged 25 to less than 65 years (14.46 ± 3.37 to 20.12 ± 5.03 m^3/day and 0.247 ± 0.061 to 0.289 ± 0.077 m^3/kg-day) are lower than those for normal-weight pregnant and lactating females aged 23 to 55 years, whose values vary from 19.00 ± 9.98 to 22.31 ± 2.50 m^3/day and 0.297 ± 0.056 to 0.330 ± 0.069 m^3/kg-day (Brochu *et al.* 2006b). Moreover, mean daily inhalation rates in boys (0.428 ± 0.098 to 0.572 ± 0.191 m^3/kg-day) and girls (0.395 ± 0.076 to 0.563 ± 0.180 m^3/kg-day) aged 0.22 to less than 10 years are higher than the highest means for under-, normal- overweight and obese gravid and breastfeeding females aged 11 to 55 years of 0.385 ± 0.110 and 0.383 ± 0.064 m^3/kg-day respectively as reported in Brochu *et al.* (2006b). This is the case in spite of 1) higher VQ means (34.2 to 36.8) used in the calculation of inhalation rates in pregnant and lactating females compared to those (30.2 and 30.8) in non gestational and non lactating individuals, and 2) similar mean H values (0.21 and 0.206 L/kcal respectively).

Based on means and percentiles of physiological daily inhalation rates calculated in the present study, children are generally expected to inhale more air pollutants per unit of weight and body surface area (i.e. in µg/kg-day and µg/m^2-day respectively) than adults during identical exposure concentrations and conditions. The same applies when males are compared to females. The new methodology developed in this study therefore illustrates that some individuals inhale more air on a daily basis (thus more air pollutants) than estimated before. In males 16.5 to less than 25 years of age, 95^{th}, 97.5^{th} and 99^{th} percentile values of 28.05, 30.02 and 31.89 m^3/day respectively were determined. In males 35 to less than 45 years old, corresponding percentiles were 29.32, 31.84 and 35.40 m^3/day respectively. Values from the 95^{th} to 99^{th} percentile in children younger than 1 year of age vary from 0.806 to 1.105 m^3/kg-day in girls and 0.842 to 1.138 m^3/kg-day in boys. These percentiles are 2.8 to 4 fold higher than the inhalation estimate of 0.286 m^3/kg-day (i.e. 20 m^3/day for a 70-kg adult) adopted by the Federal Register (1980). The same nearly applies to the span of values from the 5^{th} to 99^{th} percentiles (0.328 to 1.138 m^3/kg-day) for children aged 0.22 to less than 7 years, and the 10^{th} to 99^{th} percentiles (0.303 to 0.712 m^3/kg-day) for those from 7 to less than 10 years old.

Finally, the use of H_F, H_P, VQβ and VQα values as calculated in the present study does not invalidate the conclusions of our previous studies based on calculations using a VQ of 27 and H of 0.21 L of O_2/kcal as constant values: 1) the aggregate errors (under- and overestimations) of daily inhalation estimates and percentiles (in m^3/day and m^3/kg-day) based on published approaches do remain the same (Brochu *et al.* 2006c), and 2) intakes of inhaled air pollutants per unit of body weight (in µg/kg-day) again are expected to be higher in normal-weight males and females compared with their overweight and obese counterparts (Brochu *et al*. 2006a, 2006b).

H values

High intakes of carbohydrates and a low level of proteins ingested led to lower H_P values (0.203 to 0.204 L of O_2/kcal) in subjects (n=17,993) living in Ghana, the Philippines and Vietnam, compared those from other countries (0.205 to 0.208 L of O_2/kcal; n=101,686). However, the magnitude of H_P values is unaffected by an individuals' age, gender or body mass index for subjects living in a given country (n=119,679). Rather, it is the variability of the food intake components that determines the magnitude of H_P values. However, such variability is found to have little effect on the magnitude of physiological daily inhalation rates. The use of the lowest H_P value of 0.203 L of O_2/kcal for Vietnamese subjects (n=17763) and the highest H_P value of 0.208 L of O_2/kcal for American and French subjects (n=77278), instead of the H_P value of 0.2059 L of O_2/kcal that was used in this study, would have changed the physiological daily inhalation rates by only -1.2 to +0.9%. This is due to the fact that H_P and H_F values (i.e. 0.2059 and 0.2057 L of O_2/kcal respectively) both rest in the middle of the span between the lower Vietnamese (i.e. 0.203 L of O_2/kcal) and higher American (i.e. 0.208 L of O_2/kcal) values. Several thousand sets of VO_2 and VCO_2 values (data not reported in Tables; n=6,696) measured in subjects during strenuous exercise when consuming higher oxygen rates (0.82 to 5.48 L/min) than upper $VO_2\beta$ and $VO_2\alpha$ limits would have biased H values were they included in the present study.

VQ values

For a given age group, VQ values during anaerobiosis were found to be higher than values for $VQ\beta$, $VQ\alpha$ and VQ for VO_2 demands below the anaerobic threshold ranging from 0.54 to 1.81 L/min. Former VQ values were calculated by using VE values measured in subjects performing strenuous exercises during high oxygen uptake rates varying from 0.86 to 4.47 L/min in children aged 1 to less than 16.5 years and 3.00 to 5.63 L/min in individuals 16.5 to 96 years of age respectively. During such periods of exertion the aerobic metabolism becomes inadequate to supply all energy required and is compensated by the anaerobic metabolism (Guyton, 1992). However, these punctual VE values as well as those used for the calculation of VQ values below the anaerobic threshold have little influence on physiological daily inhalation rates, since $VO_2\alpha$ values during the aggregate daytime activities for subjects aged 2.6 months to 96 years were found to vary only from

0.06 to 0.81 L/min. The performance of activities under anaerobic conditions can be considered to correspond, in the reality of each day, to sufficiently rare events of short durations; the latter are therefore diluted in the large aerobic process of oxygenation, which is continuously effective during the aggregate daytime activities as well as on a 24-hour basis. Consequently, values for VQ during anaerobiosis would have overestimated physiological daily inhalation rates, while most of those during sub-anaerobiosis would have underestimated such rates.

CONCLUSION

This study presents an exhaustive compilation and critical analysis of a wide range of published data related to H and VQ values. It supports the establishments of solid bases for the appropriate selection and use of input data in the determination of daily inhalation rates. By the same occasion, it contributes to improve our previous procedure based on DLW measurements (Brochu *et al*. 2006a, 2006b. 2006c) due to the fact that it is now possible to determine and integrate nighttime and daytime respiratory parameters into the physiological daily inhalation calculation process. Only data measured in healthy subjects during VO_2 demands within the span of $VO_2\beta$ and $VO_2\alpha$ values based on DLW measurements were used in the present study in order to determine H_F and VQβ values for nighttime sleep (fasting phase) as well as H_P and VQα values for aggregate daytime activities (postprandial phase) respectively. This innovative strategy has allowed for the exclusion of inadequate published data in the calculation of physiological daily inhalation rates measured in more than nineteen thousands subjects. Values for H_F, VQβ, H_P and VQα were combined into the daily inhalation rates calculation process with BEE from indirect calorimetry measurements (n=1235) as well as ECG and TDEE values based on DLW methodology covering an aggregate period of more than 19, 000 days. In the worst case scenario, simultaneous minimal and maximal mean errors associated with H, BEE, ECG and TDEE values could have a combined effect varying from -3.0 to +2.3% on the accuracy of physiological daily inhalation values. This span of potential errors is insignificant compared to those based on time-activity-ventilation, food-energy intakes, metabolic equivalents and Parameter A approaches (Brochu *et al.* 2006c) which vary from -49 to +122% for some 24-hour breathing estimates. Body weight and height, as well as BEE and TDEE values that have been systematically measured for each subject during

DLW measurements have assured a precise calculation of inhalation rates per unit of weight and body surface area in the present study. Mean and percentile physiological daily inhalation rates expressed in m^3/m^2-day have never been determined before for individuals as a function of age. The information presented strongly suggests that the mean and percentile physiological daily inhalation values reported in this study correspond to the most precise inhalation values (in m^3/day, m^3/kg-day and m^3/m^2-day) in current literature, and are thereby recommended for use in health risk assessment.

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APPENDIX I

VO_2 and VE measurements reported in the following studies were used to calculate the VQ values of Table 6. Values for VO_2 and VCO_2 taken from the underlined references were also used to determine the H values. Bibliographical details of the following references are described in Brochu *et al.* (2010c)

Individual data from Robinson (1938), Åstrand (1952), Cohn *et al.* (1954), Cook *et al.* (1955), Craig (1955), Stahlman and Meece (1957), Åstrand *et al.* (1959), Åstrand and Saltin (1961a, 1961b), Becklake *et al.* (1962), Donevan *et al.* (1962), Nelson *et al.* (1962), Newman *et al.* (1962), Andersen and Hart (1963), Cander and Hanowell (1963), Mostyn *et al.* (1963), Pugh *et al.* (1964), Tabakin *et al.* (1964), Michael and Horvath (1965), Damato *et al.* (1966), Karlsson *et al.* (1967), Ekblom *et al.* (1968), Pierce *et al.* (1968), Murphy *et al.* (1969), Ouellet *et al.* (1969), Costill *et al.* (1971), Holmér (1972), Bachofen *et al.* (1973), Casaburi *et al*. (1977), Kobayashi *et al.* (1978), Jones *et al.* (1979), Frostell *et al.* (1983), Martin *et al.* (1982), Torre-Bueno *et al.* (1985), Babb and Rodarte (1993), Eldridge *et al.* (2004) and Ong *et al.* (2004).

Mean values and standard deviations from Åstrand (1960), Brouha *et al.* (1960), Durnin *et al.* (1960), Froeb (1962), Raine and Bishop (1963), Naimark *et al.* (1964), Andersen and Hermansen (1965), Becklake *et al.* (1965), Hermansen and Andersen (1965), Andrew *et al.* (1966), Malmberg (1966), Knuttgen (1967), Sinning and Adrian (1968), Ekblom (1969), Hermansen and Saltin (1969), Whipp and Wasserman (1969), Dixon and Faulkner (1971), Eriksson *et al.* (1971), Godfrey *et al*. (1971), Pollock *et al.* (1971), Krone *et al.* (1972), Miyamura and Honda (1972), Åstrand *et al.* (1973), Hanson (1973), Koch and

Eriksson (1973), Davies *et al.* (1975), Drinkwater *et al.* (1975), Stamford (1975), Kearney *et al.* (1976), Weber *et al.* (1976), Sharma *et al.* (1977), Sidney and Shephard (1977), Yamaji and Miyashita (1977), Fohlin *et al.* (1978), Kanstrup and Ekblom (1978), Davis *et al.* (1979), Plowman *et al.* (1979), Segal and Brooks (1979), Heath *et al.* (1981), Inbar *et al.* (1981), Sargeant *et al.* (1981), Ehrsam *et al.* (1982), Flandrois *et al.* (1982), Miyamoto *et al.* (1982), Nery *et al.* (1982), Zimmerman *et al.* (1982), Buchfuhrer *et al.* (1983), Heigenhauser *et al.* (1983), Lewis *et al.* (1983), Toner *et al.* (1983), Anton-Kuchly *et al.* (1984), Veicsteinas *et al.* (1984), Andersen *et al.* (1985), Hagberg *et al*. (1985), Yerg *et al*. (1985), Joyner *et al.* (1986), Vogel *et al*. (1986), Wagner *et al.* (1986), Caiozzo *et al.* (1987), Hagberg *et al*. (1988), Sue *et al.* (1988), Bebout *et al.* (1989), Miyamoto *et al.* (1989), Makrides *et al.* (1990), Marti and Howald (1990), Rogers *et al.* (1990), Babb *et al.* (1991), Blackie *et al.* (1991), Kohrt *et al.* (1991), Roca *et al.* (1992), Kastello *et al.* (1993), Stevenson *et al.* (1994), Kasch *et al.* (1995), McClaran *et al.* (1995), Rowland and Boyajian (1995), Gore *et al.* (1996), Podolsky *et al.* (1996), Proctor and Beck (1996), Rowland and Cunningham (1997), Tanaka *et al.* (1997), Harms *et al.* (1998), Marven *et al*. (1998), Putman *et al.* (1998), Katayama *et al.* (1999), Pellegrino *et al.* (1999), , Hunter *et al.* (2000), Nottin *et al.* (2000), Loftin *et al.* (2001), Riddell *et al.* (2001), Schiller *et al.* (2001), Poole *et al.* (2002), Neder *et al.* (2003), Ocel *et al.* (2003), Pimentel *et al.* (2003), Volianitis *et al.* (2003), Olfert *et al.* (2004), Petersson *et al.* (2004), Nourry *et al.* (2005), Osborne and Schneider (2005), Stickland *et al.* (2006) and Woo *et al.* (2006).

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Table 1 Anthropometric, energetic measurements and oxygen consumption rates in healthy normal-weight males and females aged 2.6 months to less than 10 years

Gender and age group (years)	n	Body weight[a] (kg) Mean ± S.D.	D	Body surface area (m^2) Mean ± S.D.	D	Energetic measurement (kcal/day) BEE[b] Mean ± S.D.	D	ECG[c] Mean ± S.D.	D	TDEE[d] Mean ± S.D.	D	Oxygen consumption rate (L/min) $VO_2\beta$[e] Min	$VO_2\beta$[e] Max	$VO_2\alpha$[e] Min	$VO_2\alpha$[e] Max
Males															
0.22 to < 0.5	28	6.6 ± 1.0	L	0.34 ± 0.03	L	387 ± 64	L	121 ± 42	L	492 ± 125	L	0.06	0.09	0.06	0.19
0.5 to < 1	37	8.8 ± 1.1	L	0.42 ± 0.03	L	532 ± 63	N	40 ± 9	L	722 ± 123	L	0.07	0.10	0.08	0.24
1 to < 2	34	10.7 ± 1.1	N	0.49 ± 0.04	N	668 ± 71	N	22 ± 4	L	890 ± 145	L	0.07	0.12	0.11	0.28
2 to < 5	25	15.3 ± 3.4	N	0.64 ± 0.10	N	846 ± 153	N	17 ± 4	L	1176 ± 274	L	0.09	0.16	0.13	0.35
5 to < 7	96	19.8 ± 2.1	L	0.79 ± 0.06	L	1012 ± 91	N	41 ± 6	L	1398 ± 192	L	0.12	0.20	0.18	0.45
7 to < 10	28	26.8 ± 4.2	L	0.98 ± 0.10	L	1129 ± 116	N	51 ± 10	L	1722 ± 322	L	0.13	0.21	0.18	0.55
Females															
0.22 to < 0.5	49	6.6 ± 0.9	L	0.34 ± 0.03	L	374 ± 53	L	117 ± 42	L	471 ± 102	L	0.06	0.09	0.07	0.20
0.5 to < 1	63	8.5 ± 1.0	L	0.41 ± 0.03	L	506 ± 67	L	38 ± 7	L	661 ± 121	N	0.06	0.10	0.07	0.24
1 to < 2	61	10.6 ± 1.4	L	0.49 ± 0.04	L	630 ± 85	L	18 ± 3	L	844 ± 160	N	0.07	0.13	0.09	0.28
2 to < 5	36	14.4 ± 3.0	L	0.62 ± 0.09	L	776 ± 132	N	19 ± 4	L	1083 ± 219	L	0.08	0.16	0.11	0.34
5 to < 7	102	19.7 ± 2.3	L	0.79 ± 0.06	L	943 ± 75	N	34 ± 5	L	1332 ± 184	L	0.12	0.17	0.16	0.39
7 to < 10	140	27.3 ± 3.6	L	0.99 ± 0.08	L	1079 ± 86	N	42 ± 7	L	1660 ± 265	L	0.13	0.20	0.19	0.51

[a]Normal-weight for children aged 2.6 months to less than 3 years with body mass index (BMIs) between the 3rd and the 97th percentiles and those aged 4 to less than 10 years with BMIs corresponding to the 85th percentile or below (IOM 2002). [b]BEE = basal energy expenditure (i.e. basal metabolic rate expressed on a 24-hour basis) measured by indirect calorimetry (IOM 2002). [c]ECG = stored daily energy cost for growth (Brochu *et al.* 2006a). [d]TDEE = total daily energy expenditure. TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for free-living individuals (IOM 2002). [e]$VO_2\beta$ and $VO_2\alpha$ = oxygen consumption rates for individuals at rest and during aggregate daytime activities respectively used for the selection of data for the calculation of H and VQ values. D = best fit distribution (i.e. lognormal or normal) according to the Anderson-Darling goodness-of-fit test performed on individual data for each age group. N=normal; L= lognormal. n=number of individuals; S.D. = standard deviation.

Table 2 Anthropometric, energetic measurements and oxygen consumption rates in healthy normal-weight males and females aged 10 to 96 years

Gender and age group (years)	n	Body weight[a] (kg)		Body surface area (m^2)		Energetic measurement (kcal/day)						Oxygen consumption rate (L/min)			
		Mean ± S.D.	D	Mean ± S.D.	D	BEE[b]		ECG[c]		TDEE[d]		$VO_2\beta$[e]		$VO_2\alpha$[e]	
						Mean ± S.D.	D	Mean ± S.D.	D	Mean ± S.D.	D	Min	Max	Min	Max
Males															
10 to < 16.5	26	43.5 ± 11.6	L	1.36 ± 0.24	L	1474 ± 287	L	89 ± 36	L	2488 ± 635	L	0.15	0.32	0.28	0.81
16.5 to < 25	25	70.5 ± 6.1	N	1.87 ± 0.10	L	1737 ± 156	N	78 ± 41	N	3132 ± 527	N	0.22	0.31	0.35	0.72
25 to < 35	46	71.3 ± 6.8	N	1.88 ± 0.12	N	1740 ± 168	L	0 ± 0		3012 ± 467	L	0.21	0.30	0.36	0.79
35 to < 45	34	70.3 ± 6.5	N	1.86 ± 0.11	N	1625 ± 148	L	0 ± 0		3008 ± 386	L	0.19	0.30	0.40	0.66
45 to < 65	17	72.3 ± 7.9	N	1.88 ± 0.14	N	1681 ± 309	L	0 ± 0		2697 ± 492	L	0.20	0.36	0.34	0.66
65 to ≤ 96	50	68.9 ± 6.7	L	1.82 ± 0.11	L	1480 ± 187	L	0 ± 0		2286 ± 437	L	0.17	0.30	0.22	0.60
Females															
10 to < 16.5	95	45.2 ± 9.1	L	1.39 ± 0.18	N	1278 ± 150	L	82 ± 25	L	2143 ± 457	L	0.15	0.27	0.20	0.73
16.5 to < 25	30	60.6 ± 5.6	L	1.68 ± 0.10	N	1385 ± 141	N	17 ± 39	N	2523 ± 294	N	0.15	0.24	0.30	0.61
25 to < 35	88	58.7 ± 6.7	L	1.64 ± 0.12	L	1346 ± 154	N	0 ± 0		2387 ± 373	L	0.15	0.26	0.24	0.68
35 to < 45	29	58.9 ± 4.8	N	1.64 ± 0.08	N	1320 ± 114	N	0 ± 0		2441 ± 334	L	0.15	0.22	0.31	0.57
45 to < 65	51	58.7 ± 4.9	N	1.63 ± 0.09	N	1211 ± 139	L	0 ± 0		2128 ± 338	N	0.14	0.24	0.23	0.57
65 to ≤ 96	45	57.2 ± 7.3	L	1.60 ± 0.13	L	1217 ± 152	L	0 ± 0		1729 ± 383	L	0.15	0.25	0.16	0.52

[a]Normal-weight for children aged 10 to 19 years with body mass index (BMI) corresponding to the 85th percentile or below and adults aged 20 to 96 years with BMIs between 18.5 and 25 kg/m^2 (IOM 2002). [b]BEE = basal energy expenditure (i.e. basal metabolic rate expressed on a 24-hour basis) measured by indirect calorimetry (IOM 2002). [c]ECG = stored daily energy cost for growth (Brochu *et al.* 2006a). [d]TDEE = total daily energy expenditure. TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gas-isotope-ratio mass spectrometry during 7 to 21-day periods for free-living individuals (IOM 2002). [e]$VO_2\beta$ and $VO_2\alpha$ = oxygen consumption rates for individuals at rest and during aggregate daytime activities respectively used for the selection of data for the calculation of H and VQ values. D = best fit distribution (i.e. lognormal or normal) according to the Anderson-Darling goodness-of-fit test performed on individual data for each age group. N=normal; L= lognormal. n=number of individuals; S.D. = standard deviation.

Table 3 Sleep duration in healthy individuals aged 2.6 months to 96 years

Gender and age group (years)	Sleep duration (hours/day) n	Mean ± S.D.
For both genders		
0.22 to < 0.5	456[a]	14.2 ± 1.9
0.5 to < 1	916[a]	13.9 ± 1.0
1 to < 2	912[a]	13.4 ± 0.8
2 to < 5	1361[a]	11.9 ± 0.6
5 to < 7	900[a]	10.8 ± 0.5
Males		
7 to < 10	919[b]	9.9 ± 1.2
10 to < 16.5	2284[b]	9.2 ± 0.8
16.5 to < 25	552[c]	8.0 ± 1.2
25 to < 35	127[c]	8.0 ± 2.0
35 to < 45	670[d]	7.2 ± 0.7
45 to < 65	1192[d]	8.0 ± 0.5
65 to ≤ 96	366[d]	8.8 ± 0.7
Females		
7 to < 10	953[b]	10.2 ± 1.0
10 to < 16.5	2168[b]	9.3 ± 0.8
16.5 to < 25	712[c]	8.5 ± 1.1
25 to < 35	172[c]	8.4 ± 1.6
35 to < 45	784[d]	8.1 ± 0.7
45 to < 65	1196[d]	8.2 ± 0.5
65 to ≤ 96	376[d]	9.1 ± 0.7

[a]Iglowstein *et al.* (2003). [b]Eisenmann *et al.* (2006).
[c]Adams (2006). [d]Adams (2006) and Bernstein *et al.* (2001).

Table 4 Postprandial oxygen uptake factor resulting from daily nutrient intakes for all ages by country

Age (years)	n	Nutrient intake contributions (%)			Oxygen uptake factor[b] (L of O_2/kcal)	Country
		Protein	Fat	COH[a]		
1 to 9	1442	17.4	20.6	62.0	0.206	Australia[c]
< 1 month to 65+	13211	17.4	20.6	62.0	0.206	Canada[d]
24 to 74	1010	21.9	15.1	63.0	0.206	China[e]
1 to 24	3147	17.7	21.8	60.5	0.206	Finland[f, g]
3 to 65+	3003	16.7	38.1	45.3	0.208	France[h]
25 to 27	57	14.1	35.0	48.3	0.207	Germany[i]
8.9	116	9.2	22.0	68.0	0.204	Ghana[f]
2 to 8	101	18.5	23.2	58.2	0.206	Greece[j]
2 to 6	99	11.9	24.8	63.3	0.205	India[k]
9 and ≥ 60	1055	17.6	17.9	64.3	0.205	Italy[f, l]
40 to 50	351	19.4	15.1	65.5	0.205	Japan[m]
2 to 8; 50 to 69	1225	16.5	26.9	56.0	0.206	Sweden[j, n]
1.3 to 9	684	13.5	35.3	51.3	0.207	The Netherlands[f, o]
8.8	114	11.7	16.0	72.0	0.204	The Philippines[f]
0.5 to 12	2026	15.4	21.8	64.4	0.205	United Kingdom[p]
1 week to 75+	74275	17.4	34.6	47.6	0.208	United States[l, q]
All ages	17763	9.8	11.4	78.9	0.203	Vietnam[r]

[a]COH = Carbohydrate. [b]H_P = postprandial oxygen uptake factor. [c]Hitchcock *et al.* (1984), Jenner *et al.* (1988). [d]NC (1977), Leung *et al.* (1984), Brault-Dubuc and Mongeau (1989). [e]Woo *et al.* (1998). [f]Knuiman *et al.* (1983). [g]Räsänen *et al.* (1985), Räsänen *et al.* (1991), Räsänen and Ylönen (1992).[h]Razanamahefa *et al.* (2005). [i]Bosy-Westphal *et al.* (2004). [j]Neiderud *et al.* (1992). [k]Narasinga *et al.* (1982). [l]Freudenheim *et al.* (1993). [m]Tokudome *et al.* (1998). [n]Riboli *et al.* 1997. [o]Hoffmans *et al.* (1986). [p]Bransby and Fothergill (1954), Margarey and Boulton (1984), Nelson *et al.* (1990), Payne and Belton (1992), Ruxton *et al.* (1996). [q]Morisson *et al.* (1980), Butte and Calloway (1981), Reichman *et al.* (1981), DHHS (1983), Gross (1983), Butte *et al.* (1984), USDA (1984), Pao *et al.* (1985), Oliveria *et al.*

Table 5 Postprandial oxygen uptake factor resulting from daily nutrient intakes for both sexes as a function of age

Age	n	Nutrient intake contributions (%)			Oxygen uptake factor[b] (L of O_2/kcal)
		Protein	Fat	COH[a]	
		Breast milk			
1week[c]	60	18.7	26.3	55.1	0.207
2 weeks[c]	60	15.3	27.9	56.8	0.206
3 weeks[c]	60	13.0	28.4	58.5	0.206
4 weeks[c]	60	11.6	30.6	57.8	0.206
5 weeks[c]	60	11.0	30.4	58.6	0.206
1 month[d]	37	9.0	33.3	57.7	0.206
1 month[e]	10	12.2	34.8	53.0	0.206
6 weeks[c]	60	10.9	31.1	58.0	0.206
7 weeks[c]	60	10.4	30.3	59.3	0.205
8 weeks[c]	60	10.2	29.4	60.4	0.205
2 months[d]	40	8.2	31.7	60.1	0.205
9 to 10 weeks[c]	60	9.9	30.1	60.0	0.205
10 to 12 weeks[c]	60	9.7	29.0	61.3	0.205
3 months[d]	37	7.9	30.4	61.8	0.205
4 months[d]	41	7.5	31.6	60.9	0.205
		Formula-fed[f]			
1 to 12 weeks	60	15.3	26.4	58.3	0.206
		Liquid and solid food[g]			
< 1 month	6	15.7	21.7	62.7	0.205
1 to 2 months	35	15.6	20.6	63.8	0.205
3 to 5 months	65	21.1	15.7	63.3	0.206
6 to 8 month	74	21.1	17.1	61.8	0.206
9 to 11 months	70	19.8	14.5	65.6	0.205
1 to 4 years	1031	18.5	20.9	60.6	0.206
5 to 11 y	1995	16.6	20.7	62.6	0.206
19 to 19 y	2232	17.3	22.8	59.9	0.206
20 to 39 y	2346	18.9	24.0	57.1	0.206
40 to 64	2722	18.8	23.2	58.0	0.206
65+	1699	18.0	21.7	60.3	0.206

[a]COH = Carbohydrate. [b]H_P = postprandial oxygen uptake factor. [c]Gross (1983). [d]Butte *et al.* (1984). [e]Butte and Calloway (1981). [f]Gross (1983). [g]Values for Canadian individuals (NC, 1977).

Table 6 Oxygen uptake factor resulting from nutrient intakes for both sexes in different countries

Age (years)	Nutrient intake contributions (%) Males n	Males Prot[a]	Males Fat	Males COH[b]	Females n	Females Prot[a]	Females Fat	Females COH[b]	Oxygen uptake factor[c] (L of O_2/kcal) Males	Oxygen uptake factor[c] (L of O_2/kcal) Females	Country
1	62	19.6	21.6	58.9	63	20.7	23.0	56.3	0.206	0.207	Australia[d]
1.5	72	18.3	21.4	60.3	70	18.8	21.8	59.4	0.206	0.206	Australia[d]
2	74	17.8	22.1	60.1	72	17.4	21.3	61.2	0.206	0.206	Australia[d]
1 to 2	23	18.1	17.4	64.5	23	17.8	15.1	54.8	0.205	0.206	Finland[e]
2	31	14.7	18.7	66.7	31	15.1	18.7	66.2	0.205	0.205	United Kingdom[f]
3	73	16.7	20.6	62.7	72	16.8	21.5	61.7	0.206	0.206	Australia[d]
3	31	15.1	18.3	66.5	42	14.8	19.0	66.2	0.205	0.205	United Kingdom[f]
3	153	18.2	19.7	62.1	128	18.3	19.7	62.0	0.206	0.206	Finland[e]
4 to 5	128	16.4	19.0	64.6	139	16.7	19.4	63.8	0.205	0.205	United Kingdom[f, g]
6	139	17.5	19.1	63.4	145	17.7	19.8	62.6	0.205	0.206	Finland[e]
6 to 9	130	17.0	20.0	63.0	116	17.0	21.3	61.7	0.205	0.206	USA[h]
7 to 10	25	13.6	19.5	66.8	26	14.2	18.7	67.1	0.205	0.205	United Kingdom[i]
9	281	17.6	21.0	61.3	263	17.7	20.9	61.3	0.206	0.206	Finland[j, k]
9.0	434	17.0	19.8	63.3	450	17.0	20.0	63.1	0.205	0.205	Australia[l]
9	133	13.8	37.0	50.0	*n.d.*	*n.d.*	*n.d.*	*n.d.*	0.207	*n.d.*	Finland[m]
9	117	13.5	38.0	49.0	*n.d.*	*n.d.*	*n.d.*	*n.d.*	0.207	*n.d.*	The Netherlands[m]
9	109	13.4	28.0	57.0	*n.d.*	*n.d.*	*n.d.*	*n.d.*	0.206	*n.d.*	Italy[m]
9	114	11.7	16.0	72.0	*n.d.*	*n.d.*	*n.d.*	*n.d.*	0.204	*n.d.*	The Philippines[m]
9	116	9.2	22.0	68.0	*n.d.*	*n.d.*	*n.d.*	*n.d.*	0.204	*n.d.*	Ghana[m]
9 to 11	196	19.4	21.9	58.7	222	18.9	21.4	59.7	0.206	0.206	USA[n]
11 to 12	76	16.0	20.3	63.8	67	15.7	21.0	63.3	0.205	0.205	United Kingdom[i]
12	274	18.0	21.7	60.2	285	17.6	20.8	61.6	0.206	0.206	Finland[j, k]
10 to 12	132	18.9	22.1	59.0	147	16.8	20.8	62.4	0.206	0.206	USA[h]
12 to 14	296	19.4	22.6	57.9	295	19.5	22.6	58.0	0.206	0.206	USA[n]
15	257	18.4	22.2	59.4	264	17.5	20.7	61.8	0.206	0.206	Finland[j, k]
13 to 15	134	18.0	23.0	59.0	110	17.8	22.0	60.2	0.206	0.206	USA[h]
15 to 18	365	20.3	23.4	56.3	374	20.1	23.1	56.8	0.207	0.207	USA[n]
18	217	18.3	22.7	59.0	264	17.5	21.1	61.3	0.206	0.206	Finland[j, k]
16 to 19	96	19.1	24.1	56.8	84	17.1	22.7	60.2	0.206	0.206	USA[h]
21.0	73	19.1	23.7	57.2	82	17.5	21.5	61.0	0.206	0.206	Finland[j, k]
19 to 22	256	22.0	24.6	53.4	300	21.5	24.1	54.4	0.207	0.207	USA[n]
23 to 35	791	21.7	24.8	53.5	952	21.6	23.9	54.5	0.207	0.207	USA[n, o]
24	59	19.9	24.6	55.4	84	18.2	21.5	60.3	0.207	0.206	Finland[j, k]
24 to< 35	117	22.2	15.8	62.1	121	23.3	16.5	60.2	0.206	0.206	China[p]
35 to 40	714	22.6	25.6	51.9	838	22.4	24.8	52.9	0.207	0.207	USA[n]
35 to 44	129	21.9	15.7	62.4	134	22.3	15.8	61.9	0.206	0.206	China[p]
40 to 50	171	19.6	14.5	65.9	180	19.2	15.7	65.1	0.205	0.205	Japan[q]
45 to 54	124	22.2	15.2	62.6	127	22.3	14.6	63.1	0.206	0.206	China[p]
51 to 64	579	22.8	25.4	51.7	715	22.6	24.4	53.0	0.207	0.207	USA[n]
55 to 74	130	20.5	13.8	65.7	128	20.7	13.8	65.5	0.205	0.205	China[p]
≥ 60	449	18.1	16.8	65.2	497	18.1	16.8	65.1	0.205	0.205	Italy[r]
≥ 60	1583	20.9	22.0	57.1	1935	20.1	20.3	59.6	0.207	0.206	USA[n, r]

[a]Prot = Protein. [b]COH = Carbohydrate. [c]H_P = postprandial oxygen uptake factor. [d]Hitchcock *et al.* (1984).[e]Räsänen and Ylönen (1992). [f]Payne and Belton (1992). [g]Margarey and Boulton (1984). [h]Morisson et al. (1980). [i]Nelson *et al*. (1990). [j]Räsänen *et al.* (1985). [k]Räsänen *et al.* (1991). [l]Jenner *et al.* (1988). [m]Knuiman *et al.* (1983); [n]Pao *et al.* (1985). [o]Oliveria *et al.* (1992). [p]Woo *et al.* (1998). [q]Tokudome *et al.* (1999). [r]Freudenheim *et al.* (1993). *n.d.* = not determined.

Table 7 Distribution type of parameters used in the calculation process of ventilatory equivalents, oxygen uptake factors and physiological daily inhalation rates

Parameter	Acronym[a]	n	Age (years)	Distribution
Oxygen consumption rate (L/min)	$VO_2β$	337[f]	0.22 to 96	Normal
	$VO_2α$	307[f]	1 to 96	Lognormal
	$VO_{2Sub\text{-}anaerobiosis}$	682[f]	1 to 96	Lognormal
	$VO_{2Anaerobiosis}$	296[f]	1 to 96	Lognormal
Carbon dioxide production (L/min)	$VCO_2β$	162[f]	0.22 to 96	Normal
	$VCO_2α$	117[f]	1 to 96	Lognormal
Minute ventilation rate (L/min)	VEβ	131[f]	0.22 to < 1	Normal
	VEβ	49[f]	1 to 96	Lognormal
	VEα	141[f]	1 to 96	Lognormal
	$VE_{Sub\text{-}anaerobiosis}$	682[f]	1 to 96	Lognormal
	$VE_{Anaerobiosis}$	296[f]	1 to 96	Lognormal
Respiratory exchange ratio (unitless)	RERβ[b]	162[f]	1 to 96	Lognormal
	RERα[b]	117[f]	1 to 96	Lognormal
Ventilatory equivalent ratio (unitless)	VQβ[c]	280[f]	0.22 to 96	Lognormal
	VQα[c]	141[f]	1 to 96	Lognormal
Oxygen uptake factor (L of O_2/kcal)	H_F[d]	102[f]	0.22 to 96	Normal
	H_P[e]	229[f]	0.22 to 96	Lognormal
Sleep duration (hour/day)	Sld	2055[g]	0.22 to 96	Lognormal

[a]β = for subjects at rest. α = during the agregate daytime activities of subjects.[b]RER = VCO_2/VO_2 ratio.
[c]VQ = VE/VO2 ratio. [c]During fasting phase. [e]During postprandial phase. [f]Best fit distribution (i.e. lognormal or normal) according to the Anderson-Darling goodness-of-fit test performed on individual data taken from studies cited in the Appendix I and Johnson *et al.* (1960), Reeves *et al.* (1961), Åstrand *et al.* (1964), Frick and Somer (1964), Emirgil *et al.* (1967), Hermansen *et al.* (1970), Jones *et al.* (1970), Pernow and Saltin (1971), Capderou et al. (1997).
[g]Lognormal distribution based on data reported in Knutson and Lauderdale (2007) and Seicean *et al.* (2007).
n=number of individual data on which the best fit distribution (i.e. lognormal or normal) has been defined.

Table 8 Ventilatory equivalents for healthy individuals aged 2 hours to 96 years at rest and during aggregate daytime activities

Age groups for both genders (years)	Ventilatory equivalents (L of air inhaled/L of O_2 consumed)[a]															
	During resting conditions[b] (VQβ)				During the aggregate daytime activities[b] (VQα)				Below the anaerobic threshold				During anaerobiosis			
	n	Mean ± S.D.	Min	Max	n	Mean ± S.D.	Min	Max	n	Mean ± S.D.	VO_2[c] Min	VO_2[c] Max	n	Mean ± S.D.	VO_2[c] Min	VO_2[c] Max
< 1	131	30.2 ± 7.6	16.7	60.8	*Same values as those for VQβ*				*Not applicable*				*Not applicable*			
1 to < 10	35	30.8 ± 0.9	25.4	46.6	*Same values as those for VQβ*				27	26.6 ± 0.9	0.54	0.70	88	36.9 ± 5.2	0.86	2.62
10 to < 16.5	145	27.7 ± 3.4	17.1	39.4	166	29.9 ± 4.2	18.9	49.2	23	30.0 ± 0.4	0.76	0.92	1282	37.6 ± 2.1	1.50	4.47
16.5 to < 25	114	27.4 ± 4.8	14.4	47.4	85	32.2 ± 6.1	21.0	100.5	459	26.9 ± 2.0	0.72	1.81	818	35.3 ± 2.3	3.00	5.63
25 to < 35	133	32.2 ± 3.1	18.0	64.0	318	32.6 ± 4.7	15.7	84.6	390	29.8 ± 2.8	0.80	1.78	535	33.6 ± 1.5	3.01	5.18
35 to < 45	60	30.6 ± 2.2	22.1	48.0	47	33.1 ± 8.6	15.3	91.5	205	26.1 ± 1.9	0.75	1.75	125	37.7 ± 1.5	3.14	4.23
45 to ≤ 96	38	30.6 ± 2.6	22.3	40.8	59	33.7 ± 7.2	16.0	76.5	89	28.7 ± 2.1	0.77	1.17	2736	35.7 ± 1.0	1.51	4.94

[a]VQ= ratio of the minute ventilation rate (VE in L/min at BTPS) to the oxygen uptake (VO_2 in L/min at STPD). The simultaneous VE and VO_2 measurements used for VQ calculations were taken from different studies which are cited in the Appendix I. [b]VO_2 values for VQβ and VQα vary from 0.06 to 0.36 and 0.06 to 0.81 L/min respectively (Tables 1 and 2).
[c]Oxygen consumption rate (in L/min). n=number of individuals; S.D.=standard deviation; Min=minimal value; Max=maximal value.

Table 9 Distribution percentiles of physiological daily inhalation rates for normal-weight males aged 2.6 months to 96 years

Age group (years)	Physiological daily inhalation rates										
	Mean ± S.D.	Percentiles									
		2.5^{nd}	5^{th}	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	95^{th}	97.5^{th}	99^{th}
						(m^3/day)					
0.22 to < 0.5	3.76 ± 1.15	2.02	2.20	2.44	2.92	3.57	4.40	5.31	5.97	6.47	7.26
0.5 to < 1	4.66 ± 1.34	2.61	2.82	3.11	3.68	4.46	5.45	6.47	7.13	7.74	8.48
1 to < 2	5.68 ± 0.85	4.24	4.39	4.61	5.05	5.61	6.25	6.86	7.20	7.45	7.75
2 to < 5	7.35 ± 1.39	5.04	5.25	5.57	6.27	7.23	8.31	9.33	9.87	10.24	10.54
5 to < 7	9.04 ± 1.21	6.95	7.21	7.54	8.17	8.94	9.81	10.64	11.18	11.68	12.28
7 to < 10	11.17 ± 1.89	8.14	8.42	8.84	9.74	10.96	12.35	13.82	14.69	15.40	16.21
10 to < 16.5	15.64 ± 3.87	9.82	10.40	11.16	12.74	15.06	17.92	21.04	22.84	24.54	26.72
16.5 to < 25	20.39 ± 4.26	13.30	14.15	15.22	17.37	20.04	22.96	25.93	28.05	30.02	31.89
25 to < 35	20.00 ± 3.78	13.84	14.54	15.52	17.30	19.55	22.27	25.15	27.00	28.52	30.54
35 to < 45	20.12 ± 5.03	12.39	13.24	14.33	16.50	19.41	22.97	26.71	29.32	31.84	35.40
45 to < 65	18.41 ± 4.25	11.86	12.60	13.51	15.30	17.80	20.90	24.05	26.39	28.33	30.75
65 to ≤ 96	15.25 ± 3.78	9.44	10.06	10.90	12.47	14.73	17.50	20.27	22.12	23.91	26.05
						(m^3/kg-day)[b]					
0.22 to < 0.5	0.572 ± 0.191	0.290	0.317	0.356	0.433	0.541	0.677	0.828	0.937	1.040	1.138
0.5 to < 1	0.536 ± 0.166	0.288	0.312	0.344	0.414	0.509	0.634	0.759	0.842	0.922	1.015
1 to < 2	0.537 ± 0.095	0.379	0.397	0.420	0.467	0.527	0.599	0.666	0.708	0.747	0.787
2 to < 5	0.493 ± 0.125	0.297	0.317	0.345	0.400	0.477	0.568	0.663	0.726	0.777	0.845
5 to < 7	0.463 ± 0.077	0.332	0.349	0.368	0.407	0.456	0.511	0.564	0.597	0.631	0.668
7 to < 10	0.428 ± 0.098	0.275	0.290	0.312	0.357	0.416	0.485	0.560	0.609	0.653	0.712
10 to < 16.5	0.383 ± 0.131	0.191	0.211	0.237	0.288	0.362	0.454	0.556	0.628	0.702	0.790
16.5 to < 25	0.290 ± 0.065	0.184	0.197	0.213	0.244	0.283	0.330	0.377	0.406	0.435	0.473
25 to < 35	0.282 ± 0.059	0.187	0.198	0.212	0.239	0.275	0.317	0.361	0.390	0.417	0.445
35 to < 45	0.289 ± 0.077	0.173	0.185	0.203	0.234	0.278	0.333	0.389	0.429	0.470	0.523
45 to < 65	0.259 ± 0.065	0.161	0.171	0.184	0.212	0.249	0.296	0.346	0.378	0.408	0.449
65 to ≤ 96	0.225 ± 0.059	0.134	0.144	0.157	0.182	0.216	0.259	0.303	0.333	0.360	0.400
						(m^3/m^2-day)[b]					
0.22 to < 0.5	10.99 ± 3.50	5.74	6.26	7.00	8.46	10.44	12.97	15.76	17.60	19.49	21.51
0.5 to < 1	11.24 ± 3.34	6.15	6.69	7.41	8.80	10.74	13.15	15.70	17.42	18.96	21.15
1 to < 2	11.68 ± 1.91	8.42	8.83	9.30	10.28	11.51	12.91	14.25	15.06	15.79	16.59
2 to < 5	11.54 ± 2.61	7.32	7.78	8.40	9.58	11.26	13.18	15.11	16.27	17.36	18.52
5 to < 7	11.53 ± 1.72	8.59	8.96	9.43	10.30	11.39	12.61	13.83	14.58	15.29	16.11
7 to < 10	11.55 ± 2.27	7.94	8.33	8.86	9.88	11.28	12.94	14.61	15.74	16.71	17.75
10 to < 16.5	11.82 ± 3.50	6.64	7.13	7.83	9.26	11.22	13.77	16.61	18.44	20.17	22.29
16.5 to < 25	10.92 ± 2.35	7.02	7.48	8.08	9.23	10.73	12.33	13.96	15.11	16.22	17.45
25 to < 35	10.64 ± 2.12	7.21	7.63	8.12	9.12	10.40	11.89	13.52	14.50	15.43	16.50
35 to < 45	10.93 ± 2.80	6.63	7.11	7.73	8.90	10.53	12.48	14.64	16.05	17.43	19.31
45 to < 65	9.88 ± 2.36	6.28	6.63	7.15	8.16	9.56	11.25	12.99	14.24	15.32	16.92
65 to ≤ 96	8.42 ± 2.13	5.14	5.50	5.95	6.86	8.12	9.67	11.23	12.25	13.29	14.78

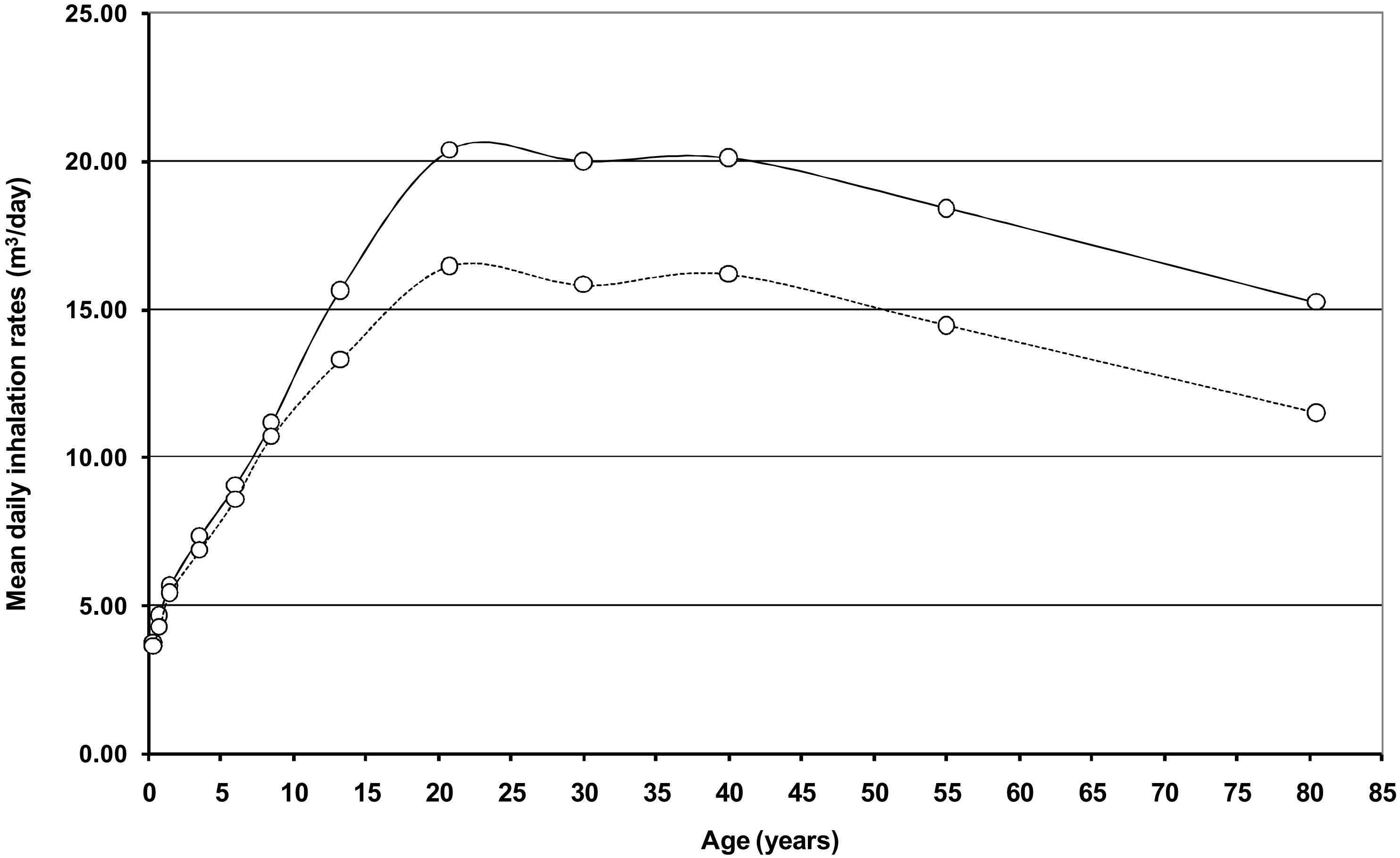
[a]Daily inhalation rates = [(SMR x H_F x VQβ x Sld) + (Eα x H_P x VQα) x (24-Sld)] x 0.06, and SMR = [(BEE x F_{sleep}) + ECG]/1440, Eα = [(TDEE-BEE)/((24-Sld) x 60)] + (BEE+ECG)/1440. BEE, ECG, TDEE (kcal/day) and Sld (hours/day) are defined and given in Tables 1 and 2. VQβ and VQα (unitless) are defined and reported in Table 8. SMR = sleeping metabolic rate (kcal/min). F_{sleep} is a correcting factor of BEE values. F_{sleep} = 0.960 ± 0.023, min.= 0.870, max.= 1.039. H_F and H_P = oxygen uptake factor during fasting and postprandial phases respectively (L of O_2/kcal). H_F= 0.2057 ± 0.0018 L/kcal, min. = 0.198 L /kcal, max. = 0.214 L /kcal. H_P = 0.2059 ± 0.0019 L/kcal, min. of 0.199 L/kcal, max.of 0.221 L/kcal. [b]Daily inhalation rates were divided by body weights and body surface areas reported in Tables 1 and 2 in order to obtain values expressed in m^3/kg-min and m^3/m^2-min respectively. S.D.=standard deviation. Min.=minimum, Max.=maximum.

Table 10 Distribution percentiles of physiological daily inhalation rates for normal-weight females aged 2.6 months to 96 years

Age group (years)	Mean ± S.D.	Physiological daily inhalation rates — Percentiles: 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
						(m^3/day)					
0.22 to < 0.5	3.63 ± 1.07	2.03	2.19	2.41	2.86	3.47	4.25	5.07	5.64	6.15	6.72
0.5 to < 1	4.30 ± 1.26	2.35	2.57	2.84	3.37	4.13	5.02	6.00	6.62	7.24	8.07
1 to < 2	5.43 ± 0.90	3.79	3.97	4.22	4.76	5.41	6.07	6.64	6.96	7.18	7.39
2 to < 5	6.90 ± 1.25	4.87	5.06	5.34	5.94	6.77	7.72	8.62	9.20	9.62	9.99
5 to < 7	8.59 ± 1.12	6.66	6.88	7.19	7.75	8.50	9.32	10.10	10.58	11.03	11.49
7 to < 10	10.71 ± 1.62	7.94	8.27	8.71	9.54	10.57	11.75	12.89	13.64	14.28	14.94
10 to < 16.5	13.32 ± 3.06	8.49	9.02	9.67	11.02	12.98	15.17	17.43	18.96	20.35	21.92
16.5 to < 25	16.46 ± 3.21	11.19	11.76	12.61	14.16	16.13	18.38	20.69	22.20	23.59	25.22
25 to < 35	15.82 ± 3.05	10.83	11.38	12.11	13.65	15.52	17.64	19.88	21.34	22.73	24.35
35 to < 45	16.21 ± 4.02	9.99	10.69	11.55	13.31	15.61	18.51	21.68	23.55	25.57	27.90
45 to < 65	14.46 ± 3.37	9.04	9.67	10.45	12.05	14.08	16.47	18.91	20.49	22.10	24.00
65 to ≤ 96	11.51 ± 3.04	6.84	7.32	7.97	9.30	11.07	13.25	15.56	17.29	18.62	20.54
						(m^3/kg-day)[b]					
0.22 to < 0.5	0.563 ± 0.180	0.299	0.326	0.360	0.431	0.534	0.662	0.807	0.897	0.994	1.105
0.5 to < 1	0.510 ± 0.159	0.269	0.295	0.329	0.393	0.486	0.601	0.722	0.806	0.882	0.979
1 to < 2	0.516 ± 0.105	0.336	0.356	0.384	0.438	0.510	0.582	0.659	0.704	0.740	0.785
2 to < 5	0.492 ± 0.124	0.288	0.311	0.341	0.400	0.480	0.568	0.661	0.716	0.766	0.826
5 to < 7	0.441 ± 0.076	0.313	0.328	0.349	0.386	0.434	0.488	0.545	0.579	0.609	0.642
7 to < 10	0.395 ± 0.076	0.267	0.284	0.303	0.340	0.388	0.443	0.497	0.531	0.564	0.601
10 to < 16.5	0.306 ± 0.089	0.170	0.185	0.204	0.241	0.293	0.358	0.427	0.471	0.514	0.566
16.5 to < 25	0.275 ± 0.059	0.180	0.190	0.206	0.234	0.269	0.310	0.352	0.380	0.408	0.444
25 to < 35	0.273 ± 0.060	0.176	0.187	0.201	0.230	0.266	0.310	0.354	0.383	0.410	0.443
35 to < 45	0.277 ± 0.072	0.166	0.179	0.194	0.225	0.266	0.318	0.373	0.410	0.443	0.480
45 to < 65	0.247 ± 0.061	0.150	0.161	0.176	0.203	0.239	0.282	0.328	0.358	0.387	0.420
65 to ≤ 96	0.202 ± 0.059	0.114	0.124	0.136	0.160	0.194	0.235	0.281	0.311	0.344	0.385
						(m^3/m^2-day)[b]					
0.22 to < 0.5	10.81 ± 3.29	5.90	6.38	7.02	8.42	10.29	12.62	15.29	17.03	18.65	20.37
0.5 to < 1	10.55 ± 3.18	5.71	6.22	6.85	8.23	10.08	12.40	14.77	16.40	17.99	20.00
1 to < 2	11.14 ± 2.06	7.47	7.91	8.49	9.61	11.04	12.55	13.93	14.74	15.40	16.10
2 to < 5	11.24 ± 2.53	7.12	7.59	8.19	9.36	10.95	12.84	14.66	15.89	16.97	18.04
5 to < 7	10.98 ± 1.67	8.12	8.49	8.93	9.77	10.84	12.03	13.24	14.00	14.60	15.41
7 to < 10	10.83 ± 1.84	7.68	8.10	8.56	9.49	10.67	12.00	13.29	14.13	14.81	15.58
10 to < 16.5	9.67 ± 2.50	5.84	6.23	6.77	7.83	9.35	11.14	13.03	14.29	15.48	16.88
16.5 to < 25	9.84 ± 2.00	6.59	6.97	7.45	8.41	9.61	11.00	12.51	13.43	14.35	15.35
25 to < 35	9.73 ± 2.01	6.43	6.84	7.33	8.30	9.52	10.93	12.41	13.32	14.27	15.27
35 to < 45	9.90 ± 2.50	6.05	6.48	7.01	8.11	9.56	11.32	13.26	14.53	15.76	17.15
45 to < 65	8.88 ± 2.12	5.46	5.87	6.35	7.35	8.62	10.12	11.69	12.75	13.67	15.00
65 to ≤ 96	7.20 ± 1.99	4.22	4.52	4.92	5.76	6.92	8.33	9.87	10.88	11.93	13.15

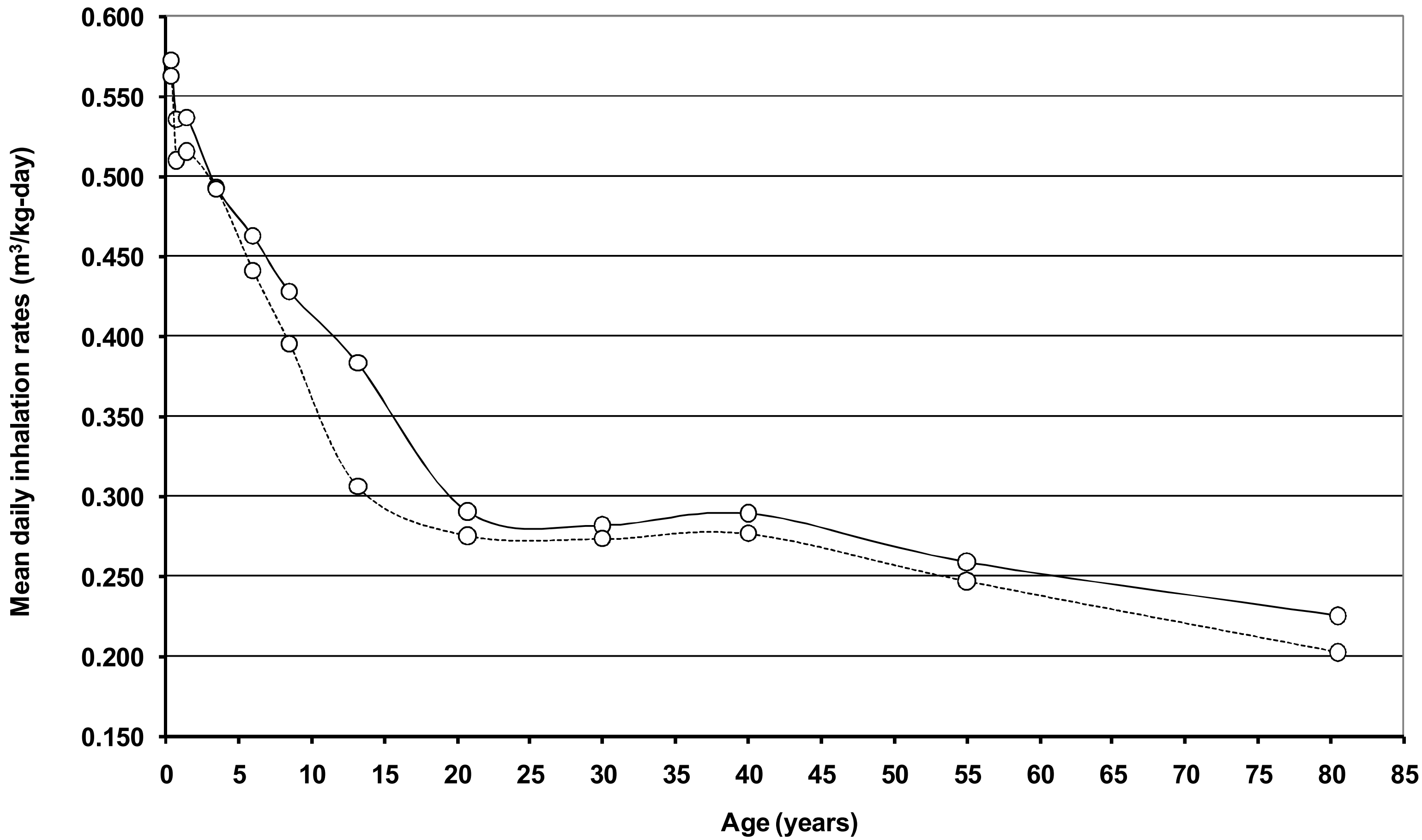
[a]Daily inhalation rates = [(SMR x H_F x VQβ x Sld) + (Eα x H_P x VQα) x (24-Sld)] x 0.06, and SMR = [(BEE x F_{sleep}) + ECG]/1440, Eα = [(TDEE-BEE)/((24-Sld) x 60)] + (BEE+ECG)/1440. BEE, ECG, TDEE (kcal/day) and Sld (hours/day) are defined and given in Tables 1 and 2. VQβ and VQα (unitless) are defined and reported in Table 8. SMR = sleeping metabolic rate (kcal/min). F_{sleep} is a correcting factor of BEE values. F_{sleep} = 0.960 ± 0.023, min.= 0.870, max.= 1.039. H_F and H_P = oxygen uptake factor during fasting and postprandial phases respectively (L of O_2/kcal). H_F= 0.2057 ± 0.0018 L/kcal, min.of 0.198 L /kcal, max.of 0.214 L /kcal. H_P = 0.2059 ± 0.0019 L/kcal, min. of 0.199 L/kcal, max.of 0.221 L/kcal. [b]Daily inhalation rates were divided by body weights and body surface areas reported in Tables 1 and 2 in order to obtain values expressed in m^3/kg-min and m^3/m^2-min respectively. S.D.=standard deviation. Min.=minimum, Max.=maximum.

Figure 1 Mean daily inhalation rates (m^3/day) in normal-weight males and females as a function of age



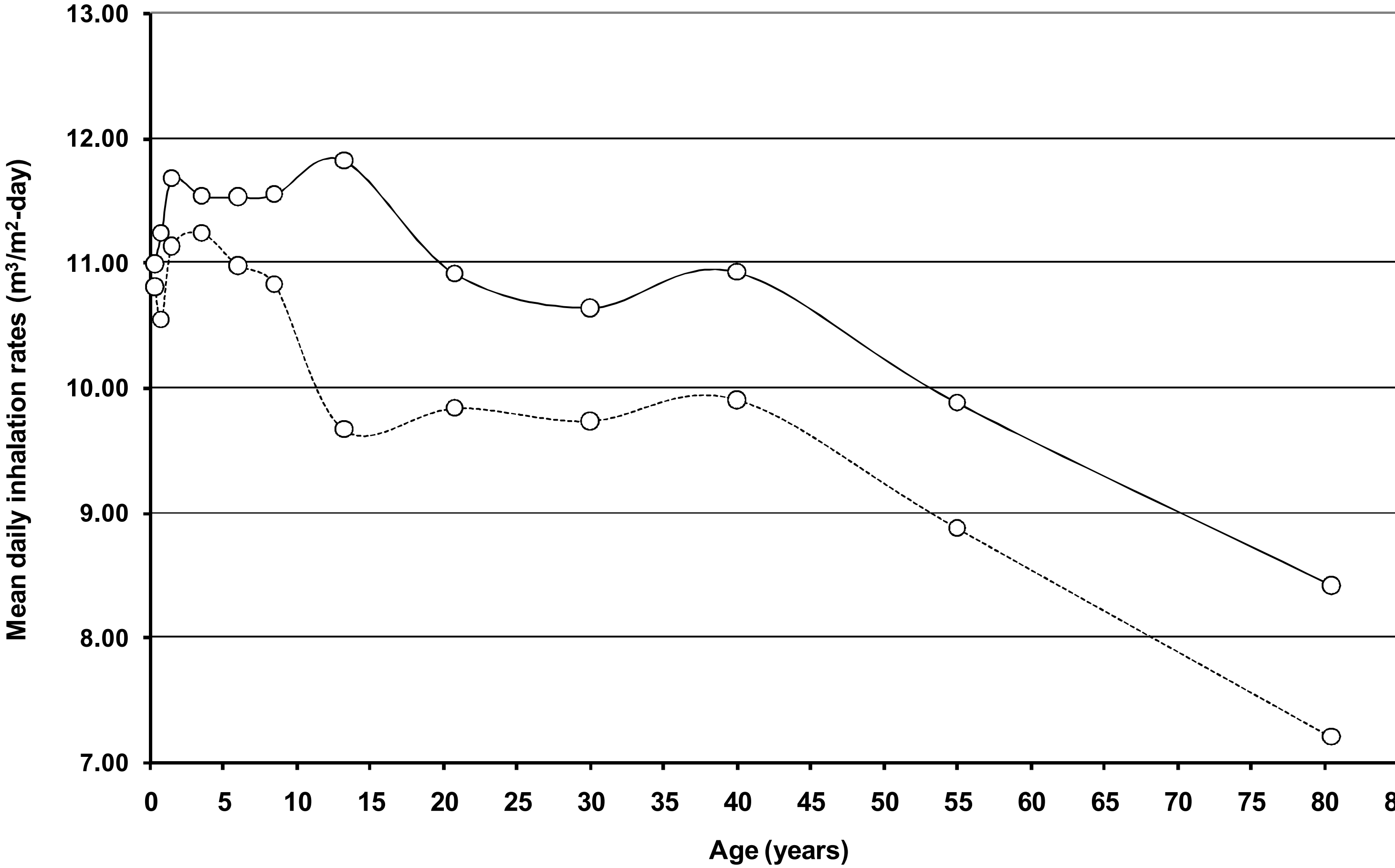
Plotted values are for midpoint ages of the age cohorts reported in Tables 9 and 10.
Males = solid line; Females = dotted line.

Figure 2 Mean daily inhalation rates (m^3/kg-day) in normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 9 and 10.
Males = solid line; Females = dotted line.

Figure 3 Mean daily inhalation rates (m^3/m^2-day) in normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 9 and 10.
Males = solid line. Females = dotted line.

CHAPITRE CINQUIÈME :

5 Article IV

Derivation of cardiac output and alveolar ventilation rate based on energy expenditure measurements in healthy males and females

DERIVATION OF CARDIAC OUTPUT AND ALVEOLAR VENTILATION RATE BASED ON ENERGY EXPENDITURE MEASUREMENTS IN HEALTHY MALES AND FEMALES

Pierre Brochu[1, 2, 3], Jules Brodeur[2] and Kannan Krishnan[2]

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[1] Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi et de l'état de l'environnement, Service des avis et expertises scientifiques, gouvernement du Québec, édifice Marie-Guyart, 7e étage, 675, boulevard René-Lévesque Est, Québec, QC, G1R 5V7, Canada.

[2] Département de santé environnementale et santé au travail, Faculté de médecine, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, QC, H3C 3J7, Canada.

[3] To whom all correspondence should be addressed.

ABSTRACT

Published indirect calorimetry measurements (n=902) and the disappearance rates of oral doses of deuterium (^2H) and heavy-oxygen (^{18}O) in urine monitored by gas-isotope-ratio mass spectrometry for an aggregate period of over 14, 000 days in the same subjects were used to determine respiratory and cardiovascular key parameters in healthy normal-weight males and females aged 5 to 96 years during their aggregate daytime activities. Arterioveinous oxygen content differences (0.051 to 0.082 ml of O_2 consumed/ml of blood) and ratios of the physiological dead space to the tidal volume (0.232 to 0.419) were determined for oxygen consumption rates (0.157 to 0.806 L/min) required by minute energy expenditures ranging from 0.76 to 3.91 kcal/min. Generally higher values for the 2.5th up to 99th percentile minute ventilation rates (0.132 to 0.774 L/kg-min, 4.42 to 21.69 L/m^2-min), alveolar ventilation rates (0.093 to 0.553 L/kg-min, 3.09 to 15.53 L/m^2-min), cardiac outputs (0.065 to 0.330 L/kg-min, 2.17 to 9.46 L/m^2-min) and ventilation-perfusion ratios (1.12 to 2.16) were found in children and teenagers aged 5 to less than 16.5 years compared to those for older individuals (0.076 to 0.461 L/kg-min, 2.80 to 16.99 L/m^2-min; 0.047 to 0.312 L/kg-min, 1.73 to 11.63 L/m^2-min; 0.045 to 0.201 L/kg-min, 1.63 to 7.24 L/m^2-min and 0.78 to 2.40 respectively). Therefore, frequently higher uptakes of liposoluble air pollutants (in µg/L of blood) by the respiratory tract in the former compared to the latter age group are expected for chemicals that have identical absorption rates and behaviours in the body for all ages.

Key words: minute energy expenditure, oxygen consumption, minute ventilation, alveolar ventilation, physiological dead space, tidal volume, arterioveinous oxygen content difference, cardiac output, blood flow, ventilation-perfusion ratio, risk assessment.

LIST OF MAIN ABBREVIATIONS

α:	data for the aggregate daytime activities of subjects
AVOD:	arterioveinous oxygen content difference
BEE:	basal energy expenditure (BMR expressed on a 24-hour basis)
BMI:	body mass index
BMR:	basal metabolic rate (punctual measurement)
BSA:	body surface area
BTPS:	body temperature pressure saturation
CaO_2:	arterial blood oxygen content
CvO_2:	venous blood oxygen content
DLW:	doubly labeled water
E:	minute energy expenditure rate
ECG:	stored daily energy cost for growth
H:	oxygen uptake factor, volume of oxygen (at STPD) consumed to produce 1 kcal of energy expended
Q:	cardiac output (also known as the blood flow rate)
Sld:	sleep duration
STPD:	standard temperature and pressure, dry air
TDEE:	total daily energy expenditure
VDphys:	physiological dead space
VT:	tidal volume
VA:	alveolar ventilation rate
VA/Q:	ventilation-perfusion ratio
VCO_2:	carbon dioxide production rate
VE:	minute ventilation rate
VO_2:	oxygen consumption rate (also known as the oxygen uptake)
VQ:	ventilatory equivalent for VO_2 (VE at BTPS /VO_2 at STPD)

INTRODUCTION

In previous publications (Brochu *et al.* 2006a, b, c, 2010a) we have developed a methodology for the determination of physiological daily inhalation rates of free-living individuals integrating both nighttime and daytime respiratory parameters, namely oxygen uptake factors (H) and ventilatory equivalents (VQ). This approach was based on published input measurements of oxygen consumption rate (VO_2), carbon dioxide production (VCO_2) and minute ventilation rate (VE) in a large number of human subjects in order to determine not only the central values but also the standard deviations of H and VQ values. The latter values were then integrated with basal daily energy expenditures (BEE) and total daily energy expenditures (TDEE), that are systematically measured using the doubly labeled water method (DLW), into the calculation process of means and distribution percentiles of physiological daily inhalation rates. This method takes into account voluntary and involuntary energy expended in unrestrained free-living subjects during the entire day (i.e. 24-hours), on a daily basis during 7 to 21 days and only requires periodic body fluid samples (usually urine or saliva) for spectrometric measurements of disappearance rates of oral doses of water isotopes (IDECG 1990).

Physiologically based pharmacokinetic (PBPK) simulation studies allow the determination of the internal dose of xenobiotics. In the case of airborne pollutants, PBPK models require, in addition to many others input parameters, cardiac output and alveolar ventilation rate (Krishnan and Anderson, 2001). PBPK and occupational exposure assessment studies are currently conducted by using strictly central VE values, alveolar ventilation rates (VA) and cardiac outputs (Q) that are not reflecting the physiological variations encountered during the aggregate daytime activities over an entire 24-hour period of activity, as well as the statistical distribution proper to a group of individuals. For example, the VE value of 20.83 L/min, notably used for occupational exposure assessments, is based on the assumption that workers inhale 10 m^3 in an 8-h workday (USEPA, 1992). Values for VA (3.83 to 5.87 L/min) and Q (4.04 to 6.73) usually used during PBPK simulation studies are those for subjects at rest (Arms and Travis 1988; USEPA 1988; Travis and Hattemer-Frey 1991; Krishnan and Andersen 2001; Price *et al.* 2003; Haddad *et al.* 2006; Valcke and Krishnan, 2009), and might not adequately reflect the uptake of airborne chemicals into the body of free-living subjects. Finally, despite the fact that variations of minute energy expenditures (E) and VO_2 values as a function of age are essential for the adequate understanding of the human physiology (Durnin and Passmore 1967; Elia 1992, 1997), the distributions of E and VO_2 percentiles have never been determined from childhood to adulthood. Overall, what precedes may represent a serious shortcoming when establishing indoor or outdoor hygienic standards for airborne toxic chemicals.

The present study is therefore intended to determine the distribution percentiles for E, VO_2, VE, Q and VA as a function of age for healthy normal-weight individuals aged 5 to 96 years during their aggregate daytime activities. In this process, we also developed equations in terms of H, VQ, BEE, and TDEE values for converting energy expenditure data into those relevant respiratory and cardiovascular parameters.

METHODOLOGY

Study Design

Published BEE and TDEE values measured in the same healthy normal-weight individuals aged 5 to 96 years (n=902) by indirect calorimetry and DLW measurements respectively and taken from the database reported in IOM (2002) were converted into E, VO_2, VE, Q, and VA values corresponding to their aggregate daytime activities (referred to as α). This was done by using six types of preliminary parameters integrated into various physiological equations. These include daily energy costs for growth (ECG), sleep durations, the oxygen uptake factor during postprandial phase (H_P), arterioveinous oxygen content difference (AVODα), ventilatory equivalents (VQα) as well as the ratios of physiological dead space to tidal volume (VDphysα/VTα ratios, unitless). Values for BEE, TDEE, ECG, sleep durations, H_P and VQα as well as body weights and heights of subjects per age group are reported in Brochu *et al.* (2010a), while values for AVODα and VDphysα/VTα ratios were determined in the present paper. For comparison purposes, VAα/Qα ratios (unitless) were calculated by using the resulting VAα and Qα values. Values for Eα, $VO_2α$, VEα, Qα, and VAα were also expressed per unit of body weight and body surface area (BSA in m^2). BSA values were calculated using the formula developed by Mosteller (1987) based on height (cm) and body weight (Bw in kg) values:

$$BSA = \left[\frac{height \times Bw}{3600}\right]^{0.5} \qquad (1)$$

Some AVODα values and VDphysα/VTα ratios were directly obtained from the literature, but most of them were calculated using published sets of Qα, $VO_2α$ and VDphysα,VTα measurements. In Brochu *et al.* (2010a), it was estimated that the oxygenation during aggregate daytime activities ($VO_2\alpha^*$) of males and females aged 5 to 96 years ranges from 0.18 to 0.81 and 0.16 to 0.73 L/min respectively. Such spans for $VO_2\alpha^*$ values were used for the adequate selection of input data from the literature. Thus, after the classification of data according to age group, solely the published AVODα, Qα, VDphysα, VTα values and the VDphysα/VTα ratios that have been measured in subjects with experimental VO_2 demands that were within the span of $VO_2\alpha^*$ values were included in the present study. These subjects were at rest, in either the sitting or standing position, or performing various activities in the upright position such as exercising on a bicycle ergometer, walking or running on a treadmill or, on a few occasions, performing muscular activities. All published values used in this study have been measured at sea level in healthy sedentary untrained and trained individuals with no history of respiratory or cardiac problems when breathing an oxygen concentration of 21%. Data for athletes and explorers were excluded from the calculation process of E, VO_2, VE, Q and VA values. Note that children and teenagers are hereafter referred to collectively as children.

Procedures of energetic measurements

The theoretical basis of indirect calorimetry is explained in Ferrannini (1988) and Bursztein *et al.* (1989), while the DLW procedure is discussed at length in IDECG (1990). Indirect calorimetry is the most accurate method (Turell and Alexander 1964) for determining BEE values based on the equation developed by Weir (1949), where gas exchange (i.e. VCO_2 and VO_2 in L/min) is monitored and nitrogen excretion from urine is measured (N in g) in subjects at rest. Values for VO_2 and VCO_2 measured by indirect calorimetry have also been used for the determination of H_P value by Brochu *et al.* (2010a). On the other hand, the DLW method measures the disappearance rates of oral doses of deuterium (^2H) and heavy-oxygen (^{18}O) in the urine or saliva of free-living subjects by gas-isotope-ratio mass spectrometry over a period of 7 to 21 consecutive days. Portions of ingested oral doses of ^2H and ^{18}O react with CO_2 to form isotopic carbonic acid which is rapidly transformed into isotopic bicarbonate ions ($^2HCO_3^-$ and $HC^{18}OO_2^-$) with the catalytic action of carbonic anhydrase. These ions leave erythrocytes to be carried out in the plasma up to the alveolar area. The reverse transformation then occurs in red blood cells where all the ^2H from the $^2HCO_3^-$ returns to isotopic water molecules (^2H_2O), while ^{18}O is returned to the $H_2{}^{18}O$; some also participate in the formation of isotopic carbon dioxide molecules ($C^{18}O_2$). It is therefore a mixture of non-isotopic (CO_2) and isotopic ($C^{18}O_2$) carbon dioxide that is exhaled. The disappearance rate of ^2H reflects water output, while that of ^{18}O represents water output as well as VCO_2 rates. Differences between the two disappearance rates can therefore be used to calculate the VCO_2 rate which is converted into TDEE values (IDECG 1990).

Accuracy of energetic measurements

Indirect calorimetry measurements of energy expenditure values are accurate within 0.6 to 0.7% by comparison with those measured by steady state direct calorimetry in a sealed chamber (or calorimeter) when urinary nitrogen excretions are considered in order to take into account the metabolism of proteins (Turell and Alexander 1964). However, as do most investigators, the present study avoids the cumbersome correction for the protein metabolism and accepts an error on BEE values varying from +1 to +2%, (Turel and Alexander 1964) and consequently an error ranging from -2 to -1% on Hp value (Brochu *et al.* 2010a). As explained by Brochu *et al.* (2010a), the mean precision of TDEE and ECG values varies from -1.0 to +3.3%. Therefore, the combined effects of, on the one hand, simultaneous mean errors associated with H_P (i.e. -2 to -1%), BEE (i.e. +1 to +2%), TDEE and ECG (i.e. -1.0 to +3.3%) values on, on the other hand, values of $VO_2\alpha$, Qα, VEα, VAα were determined in the present study.

Eα, $VO_2\alpha$ and VEα values

Precise values for $VO_2\alpha$ compared to $VO_2\alpha^*$ (L/min) were calculated in this study as well as minute energy expenditures (Eα in kcal/min) and VEα values (L/min). According to Brochu *et al.* (2010a), these values can be expressed in terms of BEE, TDEE, ECG (kcal/day) and sleep durations (Sld in hour/day) values by using the following equations:

$$E\alpha = \left[\frac{TDEE - BEE}{(24 - Sld) \times 60}\right] + \left[\frac{BEE + ECG}{1440}\right] \quad (2)$$

$$VO_2\alpha = \left[\frac{(TDEE - BEE)}{(24 - Sld) \times 60} + \frac{(BEE + ECG)}{1440}\right] \times H_p \quad (3)$$

$$VE\alpha = \left[\frac{(TDEE - BEE)}{(24 - Sld) \times 60} + \frac{(BEE + ECG)}{1440}\right] \times H_P \times VQ\alpha \quad (4)$$

where 1440 and 60 are the conversion factors from days to minutes and hours to minutes respectively and 24 is the number of hours in a day.

Value for ECG must be added to BEE in order to take into account the energy requirements for the growth process from birth to adulthood (Brochu *et al.* 2006a). H_P is the volume of oxygen consumed (at standard temperature and pressure, dry air, STPD) to produce 1 kcal of energy expended during the postprandial phase. VQα is the ratio of the VEα value (at body temperature and saturated with water vapour, BTPS) to the $VO_2\alpha$ value (at standard temperature and pressure, dry air, STPD), or $VE\alpha/VO_2\alpha$ ratio (unitless). The value for H_P of 0.2059 ± 0.0019 L of O_2/kcal (n=1245) and VQα values varying from 29.9 ± 4.2 to 32.9 ± 6.4 (n=826) according to age group were obtained from Brochu *et al.* (2010a).

Q values

The Fick principle (Fick, 1870) is one of the cornerstones of human cardiovascular physiology. The physiological mass balance between whole body $VO_2\alpha$ (L/min), Qα (L/min) and the arterial (CaO_2) and mixed venous (CvO_2) blood oxygen contents (ml of O_2/ml of blood), is outlined by the eponymous Fick principle as follows:

$$VO_2\alpha = Q\alpha \times (CaO_2 - CvO_2) = Q\alpha \times AVOD\alpha \quad (5)$$

where,

AVODα = O_2 extraction (i.e. arterioveinous oxygen content difference)

Therefore,

$$Q\alpha = \left[\frac{(TDEE - BEE)}{(24 - Sld) \times 60} + \frac{(BEE + ECG)}{1440} \right] \times \frac{H_P}{AVOD\alpha} \quad (6)$$

VA values

Values for VDphys (Bohr 1891; Enghoff 1938) include volumes of the conducting airway referred to as anatomical dead space (Fowler 1948; Folkow and Pappenheimer, 1955) and some underperfused alveoli (known as the alveolar dead space) not contributing to gas exchange (Guyton, 1991). The VA is defined as the fraction of the inspired tidal volume per minute (VT multiplied by the respiratory frequency, known as the f value) which participates in gas exchange (Guyton, 1991). The VAα (L/min) is related to the VTα (L), VDphysα (L), f (number of breaths per minute) and VEα (L/min) values by the following equations (Guyton, 1991):

$$VA\alpha = (VT\alpha - VDphys\,\alpha) \times f\alpha \tag{7}$$

$$VA\alpha = VE\alpha \times \left[1 - \frac{VDphys\alpha}{VT\alpha}\right] \tag{8}$$

Therefore, VAα in this study was computed as follows:

$$VA\alpha = \left[\frac{(TDEE - BEE)}{(24 - Sld) \times 60} + \frac{(BEE + ECG)}{1440}\right] \times \left[1 - \frac{VDphys\alpha}{VT\alpha}\right] \times H_P \times VQ\alpha \tag{9}$$

Sleep durations

Values for sleep durations in individuals aged 5 to 96 years (n=13,371) taken from Brochu *et al.* (2010a) were used in the present study regardless of the proportions of under-, normal-weight, overweight and obese individuals in the cohorts. As showed in Brochu *et al.* (2010a), several publications have reported a correlation between sleep curtailment and a higher body mass index (BMI) in children and adults, while others are challenging the view that sleep duration in subjects is inversely related to BMI increases. Therefore, the influence of shorter sleep durations of overweight and obese subjects on the order of magnitude of $VO_2\alpha$, Qα, VEα, VAα values and VA/Qα ratios were determined using the calculation process developed by Brochu *et al.* (2010a). A first set of data was calculated by using sleep durations reported for a cohort of children aged 7.5 to 16.5 years

(Eisenmann *et al.* 2006; n=3,410) and another of adults 35 to 74.5 years (Bernsteins *et al.* 2001; n=6,324) for which the proportions of normal-weight, overweight and obese individuals were known. These data were then compared to a second set of values that was calculated when initial sleep durations for 60% of overweight/obese children, and 35% of overweight as well as 55% of obese adults were decreased by 25%. This calculation corresponds to the worst case scenario of sleep durations decrease associated with overweight and obese individuals according to current literature. Further information regarding such calculation scenario is presented in Brochu *et al.* (2010a).

Statistical analysis

The best fit distributions (i.e. lognormal or normal) for TDEE, BEE, ECG, sleep durations, body weight, BSA, H_P and VQα values have been presented in Brochu *et al.* (2010a). Anderson-Darling goodness-of-fit tests were carried out on individual Qα, AVODα and VAα values, as well as VDphysα/VTα ratios from the literature in order to determine their best fit distribution (Cook *et al.* 1955; Stahlman and Meece 1957; Johnson *et al*. 1960; Reeves *et al.* 1961a; Becklake *et al.* 1962; Donevan *et al.* 1962; Nelson *et al*. 1962; Åstrand *et al.* 1964; Frick and Somer 1964; Tabakin *et al*. 1964; Beaudry *et al*. 1966; Damato *et al*. 1966; Ekblom *et al.* 1968; Ouellet *et al.* 1969; Hermansen *et al*. 1970; Jones *et al.* 1970; Pernow and Saltin 1971; Frostell *et al.* 1983; Torre-Bueno *et al.* 1985).

Means, standard deviations (S.D.) and distribution percentiles were calculated for AVODα, Eα, VO_2α, Qα, VEα and VAα values as well as VDphysα/VTα and VA/Qα ratios. Monte Carlo simulations were conducted based on random sampling involving 10,000 iterations for each calculation process. Distributions were truncated at the minimal and maximal observed values based on a critical analysis of the data compiled from an exhaustive review of the literature. This was done to eliminate from Monte Carlo simulations any outliers that did not remain within the bounds of physiological constraints.

RESULTS

Mean and S.D. values as well as distribution percentiles of AVODα, VDphysα/VTα, Eα, VO_2α, VEα, Qα, VAα and VAα/Qα for subjects aged 5 to 96 years are reported in Tables 1 to 8 respectively. Mean values as a function of age for Eα and VO_2α, as well as those for VEα, Qα and VAα are presented in Figures 1 to 3 and 4 to 6 respectively. Compared to rates expressed per unit of body surface area, those expressed per unit of body weight gradually decrease with age: values for Qα are reduced by 45 and 50% respectively, while Eα, VO_2α, VEα, VAα decrease by 51 to 59% from 5 to 96 years (Tables 3 to 7).

Individual Qα (n=129) and AVODα (n=129) values were found to have a better fit with lognormal distributions according to Anderson-Darling goodness-of-fit tests, compared to individual values for VAα and VDphysα/VTα ratios which better correspond to normal distributions (data not shown in Tables). Values for AVODα associated to VO_2α values were found to vary from 0.059 ± 0.003 to 0.073 ± 0.004 ml of O_2/ml of blood (Table 1). Values for VDphysα/VTα ratios that were calculated based on simultaneous VDphysα and VTα measurements for healthy subjects free from cardiac and pulmonary diseases (Table 2) correspond to VAα/VEα ratios (i.e. 1-VDphysα/VTα) varying from 0.619 ± 0.018 to 0.706 ± 0.032.

A 25% reduction in sleep durations for 60% of overweight/obese children, 35% of overweight adults and 55% of their obese counterparts has decreased VO_2α, Qα, VEα and VAα values of the entire cohorts by only 0.5% in boys, 0.6 to 0.7% in girls and 1.2 and 1.0 % in adult males and females respectively, while VA/Qα ratios were not altered (data not presented in Tables).

Maximum mean errors associated with H_P (-1%), BEE (+2%), ECG and TDEE values (+3.3%) resulted, when combined, in increasing Eα, $VO_2\alpha$, Qα, VEα, VAα values by -2.8 to +3.9%. An inverse scenario was observed with minimum mean errors for H_P (-2%), BEE (+1), ECG and TDEE (-1.0%) values, affecting Eα, $VO_2\alpha$, Qα, VEα, VAα values by -1.9 to +4.0%. Variations of H_P, BEE, TDEE and ECG values did not alter the magnitude of the VAα/Qα ratios (data not given in Tables).

DISCUSSION

The respiratory and cardiovascular parameters determined in the present study are consistent with the range of published values. VAα/Qα ratios reported in this study (or VAα and Qα values) are in agreement with the known values in subjects in the upright position when their experimental VO_2 demands are within the span of $VO_2\alpha$ values. This concordance is reflective of the adequacy of the processes and sets of input parameters used for the determination of VAα and Qα values (i.e. VEα, VDphysα/VTα and $VO_2\alpha$, AVODα respectively), and of course for the calculation of VEα (i.e. Eα, H_P, VQα) as well as $VO_2\alpha$ (i.e. Eα, H_P). For instance, mean and individual VA/Q ratios reported in the literature for resting adults range from 0.74 ± 0.09 to 0.87 ± 0.28 (n=77) and 0.58 to 1.13 (n=20) respectively (Farhi and Rahn 1955; West and Dollory 1960; West 1962; Lenfant 1963; Ayres *et al*. 1964; Johnson and Miller 1968; West *et al*. 1974; Zwart *et al*. 1976; Frostell *et al*.1983; Rhodes *et al.* 1989; Yem *et al*. 2006). The span of these ratios is in accordance with values of the gap between the 2.5th and 10th percentile VAα/Qα ratios varying from 0.78 to 1.09 for individuals aged 16.5 to less than 96 years with associated $VO_2\alpha$ values (0.157to 0.426 L/min); this matches well with typical published VO_2 demands (0.236 to 0.454 L/min) for resting subjects (n=46) aged 19 to 81 years (Damato *et al.* 1966; Bachofen *et al.* 1973). Spans of VAα/Qα ratios from the 2.5th to 99th percentile in individuals aged 16.5 to less than 25 years and from 10th to 99th percentile in those 35 to less than 45 years of age range from 0.91 to 2.14 (VEα from 9.22 to 30.41) and 0.92 to 2.40 (VEα from 9.28 to 31.39 L/min) respectively. By comparison, VA/Q ratios vary from 0.90 to 2.45 based on VA and Q values measured in females aged 20 to 30 years (n=8) inhaling about the same volume of air varying from 9 to 31 L/min (Olfert *et al.* 2004).

These 99th percentile VAα/Qα ratios of 2.14 and 2.40 for VEα of 30.41 and 31.39 L/min respectively are also consistent with the higher value of VA/Q ratio of 2.61 resulting from measurements in men aged 20 to 30 years (n=7) when they were performing activities requiring the higher VE value of 38.2 L/min (Olfert *et al.* 2004). The 99th percentile VAα/Qα ratio of 1.93 for $VO_2α$ ranging from 0.648 to 0.796 L/min in individuals aged 25 to less than 35 year is confirmed by VA/Q ratios ranging from 2.00 to 2.01 based on simultaneous VA and Q measurements in females aged 23.6 to 30.2 years (n=17) by Hopkins *et al.* (2000) during slightly higher VO_2 demands (0.79 to 0.83 L/min). No published VAα/Qα ratio is available for older individuals. However, VEα values used to calculate VAα values as well as Qα values for older individuals are in agreement with published values. Spans of VEα values in males and females aged 45 to less than 65 years between the 2.5 to 99th percentile range from 6.78 to 28.06 L/min ($VO_2α$ from 0.240 to 0.671 L/min),while those in males 65 to 96 years old vary from 4.52 to 25.16 L/min ($VO_2α$ from 0.157 to 0.611 L/min). Such VEα values are in accordance with published VE values varying from 5.6 to 32.3 L/min (VO_2 from 0.236 to 0.797 L/min) in adults aged 45 to 63 years (n=40) and 5.71 to 25.1 L/min (VO_2 from 0.167 to 0.673 L/min) in males 65 to 91 years old (n=29) respectively (Robinson 1938; Cohn *et al.* 1954; Tenney and Miller 1956; Raine and Bishop 1963; Damato *et al.* 1966; Bachofen *et al.* 1973; Nery *et al.* 1982; Frostell *et al.* 1983). The span between the 25th and 99th percentile Qα values for individuals aged 45 to 96 years ranging from 3.89 to 11.65 L/min ($VO_2α$ from 0.230 to 0.671 L/min) agrees with published values ranging from 3.7 to 12.30 L/min (VO_2 from 0.202 to 0.647 L/min) for subjects aged 45 to 73 years (Reeves *et al.* 1961a; Damato *et al.* 1966; Emirgil *et al.* 1967; McGuire *et al.* 2001; n=48).

Regarding children aged 10 to less than 16.5 years, the 2.5th percentile VAα/Qα ratio of 1.12 (VO_2α from 0.229 to 0.266 L/min) is in agreement with those varying from 1.07 to 1.17 estimated on the basis of ratios varying from 0.85 to 0.93 for boys aged 11 to 13 years (n=9) in the supine position during VO_2 demands ranging from 0.24 to 0.25 L/min (Koch and Ericksson 1973). The latter ratios were increased by 25.3% in order to compensate for the proportional decrease of blood flow that is observed when subjects change from a supine to an upright position (Reeves *et al.* 1961a; Damato *et al*. 1966; Hossack and Bruce 1982; Gisolf *et al*. 2003). Our 99th percentile VAα/Qα ratio value of 2.16 for the same age groups (VO_2α from 0.681 to 0.806 L/min) is consistent with higher VA/Q ratio of 2.49 measured for boys (n=9) in the sitting position during much higher VO_2 requirements of 1.14 L/min (Koch and Ericksson 1973). The gap between these lower and upper limits of VA/Q ratios varying from 1.07 to 2.49 based on data reported in Koch and Ericksson (1973) confirms the magnitude of the span between the 2.5th and 99th percentile VAα/Qα ratios ranging from 1.12 to 2.16 in children aged 10 to less than 16.5 years. The magnitudes of VAα and Qα values for younger children are confirmed by published measurements. For instance, the span between the 25th and 90th percentile VAα values ranges from 5.26 to 8.63 (VO_2α from 0.259 to 0.417 L/min) in children aged 7 to less than 10 years. By comparison, VA values varying from 5.03 to 9.03 L/min have been measured in those aged 6 to 17 years (n=56) during comparable VO_2 demands ranging from 0.262 to 0.389 L/min (Zapletal *et al.* 1987). The 97.5th percentile Qα values of 6.73 L/min in boys and 6.23 L/min in girls aged 7 to less than 10 years for VO_2α of 0.487 and 0.446 L/min respectively are also in accordance with mean values of 6.8 L/min in males (n=12) and 6.60 L/min in females (n=12) aged 7 to 9 years that have been measured during light activities with VO_2 demands of 0.55 and 0.51 L/min respectively (Turley and Wilmore 1997a).

As expected, mean VAα/Qα ratios in children aged 5 to less than 16.5 years (1.49 ± 0.12 to 1.53 ± 0.24) are higher than those for older individuals 16.5 to 96 years old (1.22 ± 0.27 to 1.36 ± 0.28). In response to higher oxygen demands associated with higher energy expenditures in children aged 5 to less than 16.5 years (0.044 ± 0.014 to 0.063 ± 0.014 kcal/kg-min, 1.40 ± 0.40 to 1.72 ± 0.56 kcal/m^2-min), when compared with lower oxygen demands in older individuals aged 16.5 to 96 years (0.025 ± 0.007 to 0.038 ± 0.007 kcal/kg-min, 0.88 ± 0.25 to 1.44 ± 0.25 kcal/m^2-min), VA (and thus VE) values increase in order to sustain adequate oxygen blood concentrations, while the Q values rise in order to increase oxygen transport to all body tissues. Higher oxygen uptakes in children compared to those in older individuals are assured by higher number of alveoli per unit of body weight and body surface area. For instance, the number of alveoli determined in children 4 and 8 years of age is 15.86 and 11.20 x 10^6 alveoli/kg, or 383.6 and 304.4 x 10^6 alveoli/m^2 respectively, compared to much lower values in adults: 3.84 x 10^6 alveoli/kg or 155.8 x 10^6 alveoli/m^2 (Dunnill 1962). These values are consistent with those reported by Davies and Reid (1970) as well as Angus and Thurlbeck (1972).

Thus, alveolar ventilation rates must maintain a relatively high level of alveolar and arterial oxygen partial pressure in order to compensate for temporary biochemical limitations that are observed in children aged 5 to less than 16.5 years compared to older individuals. Lower blood haemoglobin concentrations and slightly higher concentrations of 2, 3-diphosphoglycerate are observed in children 5 to less than 10 years old compared to those aged 10 to less than 16.5 years (Motoyama *et al.* 1990). Higher concentrations of 2, 3-diphosphoglycerate in red cells increase the oxygen unloading from haemoglobins at the tissue level (Oski and Delivoria-Papadopoulos, 1970; Card and Brain, 1973; Oski 1973, Motoyama *et al.* 1974). Mean haemoglobin levels for children aged 2 to 5, 6 to 8, 10 to 12 and 14 to 16 years are 11.9 ± 1.2 (n=22), 12.6 ± 0.8 (n=41), 13.2 ± 0.9 (n=54) and 14.4 ± 1.4 g/dl (n=34) in boys and 12.4 ± 0.9 (n=20), 12.7 ± 1.0 (n=10), 13.2 ± 1.0 (n=29) and 13.4 ± 1.2 g/dl (n=15) in girls respectively (Spurr *et al.* 1992). These values which are in agreement with other blood haemoglobin concentrations varying from 12.99 ± 0.31 to 13.9 ± 1.3 g/dl (n=186) for children 7 to 13.7 years of age (Åstrand 1952; Eriksson *et al.* 1971; Koch and Ericksson 1973; Turley and Wilmore 1997a, 1997b; Obert *et al*. 2003; Vinet *et al.* 2003) are lower than those for adults aged 18 to 89 years (n=504) ranging from 13.00 ± 1.25 to 15.9 ± 1.2 g/dl (Rotta *et al.* 1956; Tenney and Miller 1956; Åstrand *et al.* 1964; Ekblom *et al*. 1968; Holmér *et al.* 1974; Kanstrup and Ekblom 1982; Bebout *et al.* 1989; Stringer *et al*. 1997; Proctor *et al.* 1998a, 1998b, 2003; Sun *et al.* 2000; Poole *et al*. 2002; Mourtzakis *et al*. 2004; Beck *et al.* 2006). Overall, immature mechanisms for oxygen transport to body tissues with higher energy expenditures in children 5 to less than 16.5 years old provide a reasonable explanation for the unique values of VA and Q proper to this age group.

CONCLUSION

The present study provides a complete and original set of key respiratory and cardiovascular parameters (i.e. Eα, AVODα $VO_2α$, VEα, Qα, VAα, values and VDphyα/VTα, VAα/Qα ratios), with their distributions, for healthy normal-weight males and females aged 5 to 96 years old during their aggregate daytime activities. As done by Brochu *et al.* (2010a) for the selection of input literature data when calculating H_P and VQα values, solely data measured in subjects in the upright position during VO_2 demands that were within the span of $VO_2α$* values were used in this study. Such a procedure assures that data included in the calculation processes of $VO_2α$, VEα, Qα, VAα, values and VAα/Qα ratios adequately describe daytime activities for individuals of different age groups. The fact that the spans of $VO_2α$ values per age group appear to be in agreement with those for $VO_2α$* provides added value to this approach.

Determination of energy expenditures during aggregate daytime activities (i.e. Eα) for each age group by subtracting published BEE from TDEE values that are measured for same subjects by the DLW method is unique. Indirect calorimetry measurements (n=902) in normal-weight males and females and disappearance rates of oral doses of water isotopes (^2H_2O and $H_2{}^{18}O$) in urine for an aggregate period of over 14, 000 days were used for the calculation of Eα values. In addition, the accuracy of $VO_2α$, VEα, Qα, VAα, values expressed in L/min, L/kg-min as well as L/m^2-min and VAα/Qα ratios is enhanced by the fact that 1) the weight and height, as well as the BEE and TDEE values used in the calculation processes were available for each subject when conducting the DLW method; 2) each TDEE value systematically encompasses voluntary and involuntary energy expended in unrestrained free-living subjects each minute of the day, 24-hours per day, on a daily basis during 7 to 21 days; and 3) in the worst case scenario, simultaneous extreme mean errors for H_P (-2 to -1%), BEE (+1 to +2%) and TDEE (–1.0 to +3.3%) values only affect Eα, $VO_2α$, Qα, VEα, VAα values by -2.8 to +4.0%.

In the present study, generally higher 2.5nd to 99th percentile VEα (0.132 to 0.774 L/kg-min, 4.42 to 21.69 L/m^2-min), and VAα values (0.093 to 0.553 L/kg-min, 3.09 to 15.53 L/m^2-min) as well as VAα/Qα ratios (1.12 to 2.16) were found in normal-weight children 5 to less than 16.5 years of age when compared with those for older individuals (VEα from 0.076 to 0.461 L/kg-min, 2.80 to 16.99 L/m^2-min; VAα from 0.047 to 0.312 L/kg-min and 1.73 to 11.63 L/m^2-min, VAα/Qα ratios from 0.78 to 2.40). All factors being equal, this will usually favor higher intakes (in µg/kg-min and µg/m^2-min) and uptakes (in µg/L of blood) of liposoluble air pollutants by the respiratory tract in younger individuals.

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Table 1 Distribution percentiles of arterioveinous oxygen content differences for aggregate daytime activities of healthy individuals aged 5 to 96 years

Age group for both gender (years)	Arterioveinous oxygen content differences[a] (ml of O_2 consumed/ml of blood)											
	n	Mean ± S.D.	Min	Max	Percentiles[b]							
					2.5nd	10th	25th	50th	75th	90th	97.5th	99th
5 to < 16.5	110	0.073 ± 0.004	0.057	0.088	0.065	0.067	0.070	0.073	0.075	0.078	0.081	0.082
16.5 to < 25	286	0.060 ± 0.005	0.049	0.076	0.051	0.054	0.056	0.060	0.063	0.066	0.070	0.072
25 to < 45	193	0.062 ± 0.004	0.048	0.078	0.054	0.057	0.059	0.062	0.064	0.067	0.070	0.072
45 to ≤ 96	30	0.059 ± 0.003	0.051	0.069	0.054	0.056	0.057	0.059	0.061	0.063	0.065	0.066

[a]Measurements reported in Johnson *et al.* (1960), Reeves *et al*. (1961a), Donevan *et al.* (1962), Åstrand *et al.* (1964), Frick and Somer (1964), Tabakin *et al.* (1964), Dagenais *et al.* (1966), Damato *et al.* (1966), Ekblom *et al.* (1968), Ouellet *et al.* (1969), Hermansen *et al.* (1970), Jones *et al*. (1970), Eriksson *et al.* (1971), Pernow and Saltin (1971), Krone *et al.* (1972), Zeidifard *et al.* (1972), Sharma *et al*. (1977), Kanstrup and Ekblom (1978), Hossack and Bruce (1982), Frostell *et al.* (1983), Lewis *et al.* (1983), Torre-Bueno *et al.* (1985), Wagner *et al.* (1986), Bebout *et al.* (1989), Miyamoto *et al.* (1989), Podolsky *et al.* (1996), Turley and Wilmore (1997a), Rice *et al.* (1999), Hopkins *et al.* (2000), Sun *et al.* (2000), McGuire *et al.* (2001), Nottin *et al.* (2002), Poole *et al.* (2002), Vinet *et al.* (2002), Gisolf *et al.* (2003), Olfert *et al.* (2004), Dibski *et al.* (2005). [b]Percentiles based on a lognormal distribution according to the Anderson-Darling test performed on individual data. n=number of individuals; S.D.= standard deviation; Min=minimum; Max=maximum.

Table 2 Distribution percentiles of ratios of physiological dead space to tidal volume for aggregate daytime activities of healthy individuals aged 5 to 96 years

Age group for both gender (years)	Ratios of physiological dead space to tidal volume[a] *(unitless)*											
	n	Mean ± S.D.	Min	Max	Percentiles[b] 2.5nd	10th	25th	50th	75th	90th	97.5th	99th
5 to < 10[c]	52	0.336 ± 0.040	0.244	0.428	0.264	0.287	0.311	0.337	0.363	0.398	0.409	0.418
10 to < 16.5[d]	81	0.294 ± 0.032	0.203	0.386	0.232	0.253	0.272	0.293	0.315	0.345	0.357	0.366
16.5 to < 25[e]	48	0.301 ± 0.026	0.220	0.386	0.250	0.268	0.283	0.300	0.318	0.343	0.351	0.361
25 to < 35[f]	112	0.329 ± 0.015	0.280	0.389	0.299	0.310	0.319	0.329	0.339	0.354	0.359	0.364
35 to < 45[g]	79	0.344 ± 0.018	0.281	0.407	0.308	0.321	0.331	0.344	0.356	0.374	0.380	0.386
45 to < 65[h]	55	0.339 ± 0.021	0.273	0.405	0.299	0.312	0.325	0.340	0.354	0.374	0.380	0.388
65 to ≤ 96[i]	36	0.381 ± 0.018	0.334	0.428	0.347	0.359	0.369	0.382	0.393	0.410	0.414	0.419

[a]VDphysα/VTα ratios. [b]Percentiles based on a normal distribution according to the Anderson-Darling test performed on individual data. [c]Kerr (1976). [d]Beaudry (1966) and Kerr (1976). [e]Mellemgaard (1966), Whip and Wasserman (1969), Olfert *et al.* (2004). [f]Froeb (1962), Malmberg 1966, Mellemgaard (1966), Whip and Wasserman (1969), Craig *et al.* (1971), Frostell *et al*. (1983), Allen *et al.* (1984), Dempsey *et al.* (1984), Olfert *et al*. (2004). [g]Froeb (1962), Malmberg (1966), Mellemgaard (1966), Craig *et al*. (1971), Dempsey *et al*. (1984). [h]Mellemgaard (1966), Craig *et al.* (1971), Frostell *et al.* (1983). [i]Tenney and Miller (1956), Mellemgaard (1966), Craig *et al.* (1971). n=number of individuals; S.D.=standard deviation; Min=minimum; Max=maximum.

Table 3 Distribution percentiles of minute energy expenditures for aggregate daytime activities of normal-weight individuals aged 5 to 96 years

Age group (years)	Minute energy expenditures[a]																	
	Males									*Females*								
	Mean ± S.D.	Percentiles								Mean ± S.D.	Percentiles							
		2.5nd	10th	25th	50th	75th	90th	97.5th	99th		2.5nd	10th	25th	50th	75th	90th	97.5th	99th
(kcal/min)																		
5 to < 7	1.22 ± 0.24	0.81	0.92	1.05	1.21	1.37	1.54	1.75	1.85	1.18 ± 0.22	0.79	0.89	1.01	1.16	1.32	1.48	1.66	1.75
7 to < 10	1.54 ± 0.36	0.96	1.10	1.27	1.50	1.76	2.03	2.36	2.54	1.48 ± 0.31	0.97	1.11	1.26	1.46	1.68	1.90	2.17	2.29
10 to < 16.5	2.27 ± 0.63	1.29	1.50	1.78	2.18	2.68	3.16	3.70	3.91	1.93 ± 0.50	1.12	1.32	1.56	1.87	2.25	2.61	3.05	3.32
16.5 to < 25	2.68 ± 0.45	1.83	2.07	2.35	2.69	3.02	3.27	3.49	3.64	2.22 ± 0.32	1.62	1.81	2.00	2.21	2.44	2.63	2.86	2.97
25 to < 35	2.55 ± 0.48	1.77	1.97	2.20	2.50	2.85	3.20	3.63	3.86	2.06 ± 0.41	1.36	1.56	1.76	2.03	2.32	2.60	2.96	3.15
35 to < 45	2.49 ± 0.33	1.92	2.07	2.24	2.48	2.72	2.94	3.14	3.23	2.08 ± 0.29	1.56	1.69	1.85	2.07	2.29	2.47	2.64	2.71
45 to < 65	2.25 ± 0.42	1.57	1.72	1.93	2.2	2.54	2.84	3.15	3.27	1.82 ± 0.34	1.17	1.37	1.57	1.81	2.05	2.28	2.52	2.63
65 to ≤ 96	1.89 ± 0.44	1.14	1.34	1.57	1.86	2.19	2.5	2.84	2.97	1.41 ± 0.39	0.76	0.92	1.12	1.37	1.65	1.96	2.27	2.39
(kcal/kg-min)[b]																		
5 to < 7	0.063 ± 0.014	0.040	0.046	0.053	0.061	0.071	0.081	0.093	0.101	0.061 ± 0.013	0.038	0.044	0.051	0.059	0.069	0.079	0.090	0.097
7 to < 10	0.059 ± 0.017	0.033	0.040	0.047	0.057	0.068	0.082	0.098	0.108	0.055 ± 0.013	0.033	0.039	0.045	0.053	0.063	0.073	0.084	0.091
10 to < 16.5	0.055 ± 0.020	0.026	0.033	0.040	0.052	0.067	0.083	0.103	0.116	0.044 ± 0.014	0.023	0.028	0.034	0.042	0.053	0.063	0.078	0.086
16.5 to < 25	0.038 ± 0.007	0.025	0.029	0.033	0.038	0.043	0.047	0.052	0.055	0.037 ± 0.006	0.026	0.029	0.033	0.037	0.041	0.045	0.050	0.053
25 to < 35	0.036 ± 0.008	0.024	0.027	0.031	0.035	0.040	0.046	0.053	0.057	0.036 ± 0.008	0.022	0.026	0.030	0.035	0.041	0.046	0.053	0.058
35 to < 45	0.036 ± 0.006	0.026	0.029	0.032	0.035	0.039	0.043	0.048	0.050	0.035 ± 0.006	0.026	0.028	0.031	0.035	0.039	0.043	0.047	0.049
45 to < 65	0.032 ± 0.007	0.021	0.024	0.027	0.031	0.036	0.041	0.046	0.049	0.031 ± 0.006	0.020	0.023	0.026	0.031	0.035	0.039	0.044	0.047
65 to ≤ 96	0.028 ± 0.007	0.016	0.019	0.023	0.027	0.032	0.037	0.043	0.046	0.025 ± 0.007	0.013	0.016	0.019	0.024	0.029	0.035	0.042	0.045
(kcal/m^2-min)[b]																		
5 to < 7	1.56 ± 0.33	1.01	1.16	1.32	1.53	1.76	1.99	2.29	2.43	1.50 ± 0.31	0.97	1.12	1.28	1.48	1.69	1.92	2.18	2.33
7 to < 10	1.59 ± 0.41	0.94	1.11	1.29	1.54	1.84	2.15	2.54	2.76	1.50 ± 0.33	0.95	1.10	1.26	1.47	1.71	1.94	2.23	2.38
10 to < 16.5	1.72 ± 0.56	0.89	1.07	1.30	1.63	2.04	2.49	3.03	3.29	1.40 ± 0.40	0.76	0.92	1.11	1.35	1.64	1.94	2.29	2.50
16.5 to < 25	1.44 ± 0.25	0.97	1.10	1.25	1.43	1.61	1.77	1.93	2.00	1.33 ± 0.20	0.95	1.07	1.18	1.32	1.46	1.59	1.74	1.82
25 to < 35	1.36 ± 0.27	0.92	1.04	1.16	1.33	1.52	1.72	1.96	2.10	1.27 ± 0.27	0.81	0.94	1.08	1.25	1.43	1.62	1.85	1.99
35 to < 45	1.35 ± 0.19	1.02	1.11	1.21	1.34	1.48	1.61	1.74	1.80	1.27 ± 0.19	0.94	1.02	1.13	1.26	1.40	1.53	1.64	1.70
45 to < 65	1.21 ± 0.24	0.82	0.91	1.02	1.18	1.36	1.54	1.71	1.81	1.12 ± 0.22	0.71	0.83	0.96	1.11	1.26	1.41	1.56	1.63
65 to ≤ 96	1.05 ± 0.25	0.62	0.73	0.86	1.03	1.21	1.39	1.59	1.68	0.88 ± 0.25	0.47	0.58	0.69	0.86	1.04	1.23	1.45	1.56

[a]Eα = [(TDEE-BEE)/((24-Sld) x 60) + (BEE+ECG)/1440], where TDEE = total daily energy expenditure, BEE = basal energy expenditure and ECG = stored daily energy cost for growth.

[b]Eα (kcal/min) were divided by body weights (Bw) and body surface areas (BSA) in order to obtain values expressed in kcal/kg-min and kcal/m^2-min respectively. [a, b]Values for TDEE, BEE, ECG (kcal/day), Sld (hours/day), Bw (kg) and BSA (m^2) are presented in Brochu *et al.* (2010). S.D.=standard deviation.

Table 4 Distribution percentiles of oxygen consumption rates for aggregate daytime activities of normal-weight individuals aged 5 to 96 years

Age group (years)	Oxygen consumption rates[a]																	
	Males									*Females*								
	Mean ± S.D.	Percentiles								Mean ± S.D.	Percentiles							
		2.5nd	10th	25th	50th	75th	90th	97.5th	99th		2.5nd	10th	25th	50th	75th	90th	97.5th	99th
(L/min)																		
5 to < 7	0.252 ± 0.050	0.167	0.189	0.216	0.248	0.283	0.317	0.360	0.381	0.242 ± 0.046	0.163	0.184	0.209	0.238	0.271	0.305	0.341	0.360
7 to < 10	0.316 ± 0.075	0.197	0.226	0.261	0.309	0.362	0.417	0.487	0.522	0.305 ± 0.063	0.199	0.229	0.259	0.300	0.345	0.390	0.446	0.472
10 to < 16.5	0.466 ± 0.131	0.266	0.310	0.366	0.449	0.551	0.650	0.763	0.806	0.397 ± 0.103	0.229	0.271	0.322	0.386	0.463	0.538	0.628	0.681
16.5 to < 25	0.552 ± 0.093	0.376	0.426	0.483	0.553	0.621	0.673	0.720	0.750	0.457 ± 0.065	0.334	0.373	0.412	0.455	0.502	0.542	0.588	0.611
25 to < 35	0.526 ± 0.099	0.364	0.406	0.452	0.515	0.586	0.658	0.747	0.796	0.424 ± 0.085	0.280	0.320	0.363	0.418	0.477	0.536	0.610	0.648
35 to < 45	0.513 ± 0.067	0.395	0.426	0.462	0.510	0.560	0.605	0.647	0.665	0.428 ± 0.060	0.321	0.349	0.382	0.426	0.471	0.509	0.544	0.559
45 to < 65	0.463 ± 0.087	0.323	0.353	0.397	0.453	0.522	0.585	0.648	0.671	0.374 ± 0.071	0.240	0.283	0.324	0.372	0.423	0.469	0.518	0.542
65 to ≤ 96	0.390 ± 0.091	0.235	0.276	0.323	0.383	0.451	0.515	0.584	0.611	0.290 ± 0.080	0.157	0.190	0.230	0.282	0.340	0.403	0.467	0.494
(L/kg-min)[b]																		
5 to < 7	0.013 ± 0.003	0.008	0.009	0.011	0.013	0.015	0.017	0.019	0.021	0.012 ± 0.003	0.008	0.009	0.010	0.012	0.014	0.016	0.019	0.020
7 to < 10	0.012 ± 0.003	0.007	0.008	0.010	0.012	0.014	0.017	0.020	0.022	0.011 ± 0.003	0.007	0.008	0.009	0.011	0.013	0.015	0.017	0.019
10 to < 16.5	0.011 ± 0.004	0.005	0.007	0.008	0.011	0.014	0.017	0.021	0.024	0.009 ± 0.003	0.005	0.006	0.007	0.009	0.011	0.013	0.016	0.018
16.5 to < 25	0.008 ± 0.001	0.005	0.006	0.007	0.008	0.009	0.010	0.011	0.011	0.008 ± 0.001	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011
25 to < 35	0.007 ± 0.002	0.005	0.006	0.006	0.007	0.008	0.009	0.011	0.012	0.007 ± 0.002	0.005	0.005	0.006	0.007	0.008	0.010	0.011	0.012
35 to < 45	0.007 ± 0.001	0.005	0.006	0.007	0.007	0.008	0.009	0.010	0.010	0.007 ± 0.001	0.005	0.006	0.006	0.007	0.008	0.009	0.010	0.010
45 to < 65	0.007 ± 0.001	0.004	0.005	0.005	0.006	0.007	0.008	0.009	0.010	0.006 ± 0.001	0.004	0.005	0.005	0.006	0.007	0.008	0.009	0.010
65 to ≤ 96	0.006 ± 0.001	0.003	0.004	0.005	0.006	0.007	0.008	0.009	0.010	0.005 ± 0.002	0.003	0.003	0.004	0.005	0.006	0.007	0.009	0.009
(L/m^2-min)[b]																		
5 to < 7	0.321 ± 0.067	0.207	0.239	0.272	0.315	0.363	0.411	0.471	0.502	0.309 ± 0.064	0.200	0.230	0.264	0.305	0.349	0.395	0.448	0.480
7 to < 10	0.328 ± 0.085	0.195	0.228	0.266	0.318	0.378	0.442	0.521	0.566	0.309 ± 0.068	0.195	0.226	0.260	0.303	0.352	0.400	0.457	0.491
10 to < 16.5	0.354 ± 0.115	0.183	0.221	0.267	0.336	0.420	0.512	0.623	0.677	0.288 ± 0.082	0.158	0.190	0.228	0.278	0.338	0.400	0.475	0.517
16.5 to < 25	0.296 ± 0.052	0.199	0.227	0.258	0.295	0.332	0.364	0.396	0.412	0.273 ± 0.042	0.195	0.220	0.244	0.271	0.301	0.328	0.359	0.375
25 to < 35	0.280 ± 0.055	0.190	0.213	0.239	0.274	0.314	0.355	0.405	0.432	0.261 ± 0.055	0.167	0.194	0.221	0.256	0.295	0.333	0.381	0.409
35 to < 45	0.278 ± 0.039	0.210	0.228	0.249	0.276	0.305	0.331	0.358	0.372	0.261 ± 0.038	0.193	0.211	0.232	0.260	0.288	0.314	0.337	0.350
45 to < 65	0.248 ± 0.049	0.170	0.188	0.211	0.243	0.281	0.317	0.353	0.373	0.230 ± 0.045	0.146	0.171	0.198	0.228	0.260	0.290	0.322	0.337
65 to ≤ 96	0.215 ± 0.052	0.128	0.151	0.177	0.211	0.249	0.287	0.328	0.346	0.182 ± 0.052	0.097	0.119	0.143	0.176	0.215	0.254	0.299	0.321

[a] $VO_2\alpha$ = [(TDEE-BEE)/((24-Sld) x 60) + (BEE+ECG)/1440] x H_P, where H_p = oxygen uptake factor. TDEE, BEE, ECG and Sld are defined in Table 3. [b] $VO_2\alpha$ (L/min) were divided by body weights (Bw) and body surface areas (BSA) in order to obtain values expressed in L/kg-min and L/m^2-min respectively. [a, b] Values for TDEE, BEE, ECG (kcal/day), Sld (hours/day), Bw (kg), BSA (m^2) and H_P (0.2059 ± 0.0019 L of O_2/kcal) are reported in Brochu *et al.* (2010). S.D.= standard deviation.

Table 5 Distribution percentiles of minute ventilation rates for aggregate daytime activities of normal-weight individuals aged 5 to 96 years

Age group (years)	Minute ventilation rates[a]																	
	Males									*Females*								
	Mean ± S.D.	Percentiles								Mean ± S.D.	Percentiles							
		2.5nd	10th	25th	50th	75th	90th	97.5th	99th		2.5nd	10th	25th	50th	75th	90th	97.5th	99th
(L/min)																		
5 to < 7	7.75 ± 1.55	5.10	5.82	6.63	7.64	8.75	9.78	11.10	11.84	7.45 ± 1.44	4.99	5.65	6.41	7.32	8.36	9.39	10.56	11.20
7 to < 10	9.74 ± 2.32	6.01	6.94	8.02	9.50	11.15	12.91	15.01	16.17	9.40 ± 1.96	6.10	7.00	7.98	9.22	10.64	12.06	13.75	14.62
10 to < 16.5	13.94 ± 4.42	7.28	8.82	10.68	13.25	16.52	20.07	24.20	26.51	11.87 ± 3.55	6.33	7.70	9.27	11.40	13.98	16.65	20.09	22.00
16.5 to < 25	17.91 ± 4.54	10.63	12.51	14.61	17.35	20.63	24.10	28.04	30.41	14.83 ± 3.48	9.22	10.73	12.33	14.40	16.91	19.45	22.66	24.50
25 to < 35	17.17 ± 4.12	10.69	12.34	14.19	16.64	19.64	22.69	26.57	29.04	13.86 ± 3.43	8.20	9.82	11.42	13.51	15.84	18.44	21.73	23.46
35 to < 45	16.95 ± 4.94	9.42	11.25	13.39	16.20	19.83	23.55	28.27	31.39	14.15 ± 4.26	7.69	9.28	11.07	13.52	16.60	19.90	23.94	26.87
45 to < 65	15.47 ± 4.40	8.64	10.41	12.29	14.86	17.95	21.39	25.77	28.06	12.51 ± 3.59	6.78	8.30	9.91	12.08	14.62	17.29	20.72	22.71
65 to ≤ 96	13.05 ± 4.17	6.55	8.23	10.03	12.45	15.41	18.63	22.95	25.16	9.69 ± 3.43	4.52	5.72	7.16	9.14	11.65	14.38	17.72	19.64
(L/kg-min)[b]																		
5 to < 7	0.397 ± 0.089	0.249	0.289	0.333	0.389	0.450	0.515	0.592	0.645	0.383 ± 0.086	0.241	0.280	0.322	0.375	0.436	0.500	0.573	0.616
7 to < 10	0.374 ± 0.107	0.209	0.251	0.296	0.359	0.435	0.520	0.623	0.693	0.348 ± 0.084	0.209	0.246	0.286	0.339	0.400	0.460	0.539	0.582
10 to < 16.5	0.341 ± 0.135	0.151	0.193	0.242	0.316	0.413	0.517	0.675	0.774	0.273 ± 0.096	0.132	0.166	0.203	0.259	0.324	0.402	0.505	0.553
16.5 to < 25	0.255 ± 0.068	0.148	0.175	0.205	0.246	0.295	0.347	0.412	0.442	0.248 ± 0.062	0.149	0.175	0.203	0.240	0.284	0.331	0.391	0.426
25 to < 35	0.242 ± 0.062	0.145	0.170	0.197	0.233	0.279	0.325	0.386	0.422	0.240 ± 0.065	0.137	0.163	0.193	0.231	0.277	0.325	0.387	0.424
35 to < 45	0.244 ± 0.074	0.132	0.159	0.191	0.232	0.286	0.343	0.415	0.455	0.242 ± 0.076	0.128	0.157	0.187	0.230	0.284	0.344	0.413	0.461
45 to < 65	0.217 ± 0.065	0.118	0.143	0.170	0.208	0.254	0.303	0.372	0.414	0.214 ± 0.063	0.114	0.140	0.168	0.206	0.251	0.299	0.357	0.399
65 to ≤ 96	0.193 ± 0.064	0.096	0.119	0.146	0.184	0.227	0.278	0.349	0.385	0.171 ± 0.064	0.076	0.098	0.124	0.161	0.206	0.257	0.322	0.356
(L/m^2-min)[b]																		
5 to < 7	9.88 ± 2.10	6.35	7.34	8.37	9.68	11.21	12.61	14.54	15.57	9.53 ± 1.98	6.18	7.08	8.11	9.34	10.75	12.17	13.87	14.86
7 to < 10	10.10 ± 2.62	5.91	6.99	8.19	9.78	11.65	13.64	16.12	17.54	9.51 ± 2.12	5.97	6.97	7.98	9.32	10.85	12.36	14.17	15.15
10 to < 16.5	10.56 ± 3.77	5.04	6.28	7.78	9.95	12.67	15.65	19.53	21.69	8.61 ± 2.76	4.42	5.43	6.57	8.19	10.21	12.28	15.05	16.64
16.5 to < 25	9.60 ± 2.49	5.58	6.68	7.79	9.28	11.09	12.90	15.21	16.54	8.85 ± 2.13	5.42	6.34	7.29	8.62	10.15	11.72	13.61	14.82
25 to < 35	9.15 ± 2.27	5.56	6.49	7.51	8.84	10.49	12.14	14.36	15.77	8.52 ± 2.19	4.95	5.96	6.95	8.29	9.78	11.42	13.41	14.81
35 to < 45	9.19 ± 2.71	5.07	6.06	7.22	8.78	10.72	12.83	15.55	16.99	8.64 ± 2.63	4.62	5.65	6.73	8.26	10.14	12.19	14.63	16.36
45 to < 65	8.30 ± 2.41	4.61	5.50	6.55	7.97	9.66	11.52	13.91	15.46	7.68 ± 2.23	4.12	5.08	6.07	7.40	9.00	10.62	12.87	14.10
65 to ≤ 96	7.21 ± 2.35	3.60	4.51	5.50	6.87	8.50	10.36	12.82	14.21	6.08 ± 2.20	2.80	3.54	4.47	5.75	7.32	9.06	11.23	12.52

[a]VEα=[(TDEE-BEE)/((24-Sld) x 60) + (BEE+ECG)/1440] x H_P x VQα, where Hp = oxygen uptake factor and VQα = ventilatory equivalent. TDEE, BEE, ECG and Sld are defined in Table 3.

[b]VEα (L/min) were divided by body weights (Bw) and body surface areas (BSA) in order to obtain values expressed in L/kg-min and L/m^2-min respectively. [a, b]Values for TDEE, BEE, ECG (kcal/day), Sld (hours/day), Bw (kg), BSA (m^2), H_P (0.2059 ± 0.0019 L of O_2/kcal) and VQα (unitless) are given in Brochu *et al.* (2010). S.D.= standard deviation.

Table 6 Distribution percentiles of cardiac outputs for aggregate daytime activities of normal-weight individuals aged 5 to 96 years

Age group (years)	Cardiac outputs[a]																	
	Males									*Females*								
	Mean ± S.D.	Percentiles								Mean ± S.D.	Percentiles							
		2.5^{nd}	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	97.5^{th}	99^{th}		2.5^{nd}	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	97.5^{th}	99^{th}
(L/min)																		
5 to < 7	3.48 ± 0.71	2.28	2.60	2.96	3.42	3.93	4.43	5.04	5.40	3.35 ± 0.66	2.23	2.53	2.86	3.31	3.77	4.23	4.77	5.05
7 to < 10	4.35 ± 1.04	2.69	3.10	3.59	4.24	4.98	5.77	6.73	7.22	4.22 ± 0.91	2.70	3.10	3.55	4.13	4.78	5.45	6.23	6.67
10 to < 16.5	6.44 ± 1.83	3.61	4.25	5.04	6.18	7.60	9.03	10.52	11.19	5.48 ± 1.45	3.11	3.72	4.41	5.33	6.39	7.45	8.78	9.48
16.5 to < 25	9.27 ± 1.71	6.14	7.02	8.01	9.23	10.46	11.53	12.66	13.23	7.68 ± 1.25	5.45	6.11	6.79	7.61	8.51	9.32	10.28	10.87
25 to < 35	8.56 ± 1.71	5.80	6.50	7.29	8.38	9.59	10.86	12.40	13.19	6.91 ± 1.46	4.43	5.13	5.88	6.79	7.79	8.84	10.12	10.89
35 to < 45	8.35 ± 1.22	6.21	6.81	7.44	8.28	9.17	10.02	10.89	11.35	6.97 ± 1.08	5.07	5.59	6.17	6.91	7.70	8.40	9.17	9.55
45 to < 65	7.85 ± 1.51	5.39	5.96	6.71	7.68	8.84	9.97	11.08	11.65	6.34 ± 1.24	4.02	4.75	5.47	6.31	7.17	7.99	8.89	9.34
65 to ≤ 96	6.61 ± 1.57	3.95	4.67	5.43	6.48	7.66	8.79	9.96	10.54	4.91 ± 1.39	2.64	3.21	3.89	4.75	5.78	6.84	8.01	8.52
(L/kg-min)[b]																		
5 to < 7	0.178 ± 0.041	0.111	0.129	0.149	0.174	0.203	0.233	0.269	0.290	0.172 ± 0.039	0.107	0.125	0.143	0.168	0.196	0.223	0.258	0.279
7 to < 10	0.167 ± 0.048	0.094	0.112	0.133	0.161	0.194	0.231	0.276	0.305	0.155 ± 0.039	0.092	0.109	0.127	0.151	0.179	0.208	0.244	0.263
10 to < 16.5	0.157 ± 0.058	0.073	0.092	0.115	0.148	0.190	0.237	0.296	0.330	0.126 ± 0.040	0.065	0.079	0.096	0.120	0.149	0.179	0.223	0.247
16.5 to < 25	0.132 ± 0.027	0.085	0.098	0.113	0.131	0.149	0.167	0.188	0.199	0.128 ± 0.024	0.087	0.099	0.112	0.127	0.143	0.159	0.180	0.192
25 to < 35	0.121 ± 0.027	0.078	0.090	0.101	0.117	0.136	0.156	0.180	0.194	0.120 ± 0.029	0.073	0.085	0.099	0.117	0.137	0.157	0.183	0.201
35 to < 45	0.120 ± 0.020	0.086	0.095	0.105	0.118	0.133	0.147	0.163	0.172	0.119 ± 0.020	0.084	0.094	0.104	0.118	0.132	0.146	0.162	0.170
45 to < 65	0.110 ± 0.024	0.072	0.082	0.093	0.108	0.125	0.143	0.162	0.172	0.108 ± 0.023	0.068	0.079	0.092	0.107	0.123	0.139	0.157	0.166
65 to ≤ 96	0.098 ± 0.025	0.056	0.067	0.079	0.095	0.113	0.131	0.152	0.163	0.086 ± 0.026	0.045	0.055	0.067	0.083	0.102	0.122	0.147	0.159
(L/m^2-min)[b]																		
5 to < 7	4.43 ± 0.96	2.82	3.26	3.74	4.35	5.03	5.71	6.57	7.01	4.29 ± 0.91	2.76	3.16	3.61	4.21	4.86	5.51	6.31	6.72
7 to < 10	4.52 ± 1.18	2.66	3.14	3.66	4.38	5.23	6.12	7.20	7.90	4.26 ± 0.98	2.66	3.08	3.55	4.17	4.85	5.57	6.50	6.93
10 to < 16.5	4.88 ± 1.60	2.49	3.02	3.68	4.63	5.82	7.10	8.57	9.46	3.97 ± 1.15	2.17	2.62	3.13	3.82	4.67	5.52	6.60	7.21
16.5 to < 25	4.97 ± 0.95	3.25	3.74	4.27	4.94	5.61	6.21	6.87	7.24	4.59 ± 0.79	3.18	3.60	4.03	4.54	5.11	5.62	6.25	6.58
25 to < 35	4.56 ± 0.95	3.02	3.42	3.87	4.45	5.13	5.85	6.72	7.19	4.25 ± 0.94	2.65	3.12	3.58	4.16	4.81	5.49	6.31	6.86
35 to < 45	4.53 ± 0.70	3.32	3.64	4.01	4.49	4.99	5.47	5.98	6.31	4.25 ± 0.69	3.05	3.39	3.75	4.21	4.72	5.17	5.66	5.93
45 to < 65	4.21 ± 0.85	2.83	3.16	3.57	4.11	4.77	5.4	6.06	6.41	3.89 ± 0.79	2.45	2.89	3.34	3.86	4.42	4.94	5.51	5.80
65 to ≤ 96	3.65 ± 0.90	2.14	2.55	2.98	3.57	4.23	4.86	5.6	5.97	3.08 ± 0.90	1.63	2.00	2.42	2.98	3.65	4.31	5.10	5.53

[a] $Q\alpha = [(TDEE-BEE)/((24-Sld) \times 60) + (BEE+ECG)/1440] \times H_P \times VQ\alpha \times AVOD\alpha^{-1}$, where H_p = oxygen uptake factor, VQα = ventilatory equivalent. AVODα = arterioveinous oxygen content differences (ml of O_2 consumed/ml of blood). Values for AVODα are given in Table 1. TDEE, BEE, ECG and Sld are defined in Table 3. [b]Qα (L/min) were divided by body weights (Bw) and body surface areas (BSA) in order to obtain values expressed in L/kg-min and L/m^2-min respectively. [a, b]Values for TDEE, BEE, ECG (kcal/day), Sld (hours/day), Bw (kg), BSA (m^2), H_P (0.2059 ± 0.0019 L of O_2/kcal) and VQα (unitless) were taken from Brochu *et al* . (2010). S.D.= standard deviation.

Table 7 Distribution percentiles of alveolar ventilation rates for aggregate daytime activities of normal-weight individuals aged 5 to 96 years

Age group (years)	Alveolar ventilation rates[a]																	
	Males									*Females*								
	Mean ± S.D.	Percentiles								Mean ± S.D.	Percentiles							
		2.5nd	10th	25th	50th	75th	90th	97.5th	99th		2.5nd	10th	25th	50th	75th	90th	97.5th	99th
	(L/min)																	
5 to < 7	5.14 ± 1.07	3.33	3.83	4.36	5.06	5.82	6.56	7.48	8.02	4.94 ± 1.00	3.25	3.71	4.22	4.86	5.58	6.28	7.13	7.55
7 to < 10	6.47 ± 1.58	3.95	4.58	5.31	6.28	7.41	8.63	10.02	10.93	6.24 ± 1.35	3.99	4.59	5.26	6.11	7.07	8.07	9.28	9.89
10 to < 16.5	9.84 ± 3.15	5.16	6.19	7.51	9.37	11.67	14.11	17.21	18.81	8.38 ± 2.53	4.45	5.41	6.55	8.05	9.85	11.79	14.27	15.77
16.5 to < 25	12.52 ± 3.22	7.38	8.71	10.20	12.11	14.44	16.86	19.76	21.50	10.37 ± 2.47	6.40	7.46	8.58	10.08	11.85	13.64	15.87	17.26
25 to < 35	11.52 ± 2.78	7.15	8.27	9.52	11.17	13.18	15.22	17.82	19.62	9.30 ± 2.30	5.48	6.57	7.67	9.06	10.61	12.38	14.59	15.86
35 to < 45	11.12 ± 3.26	6.16	7.36	8.76	10.64	13.04	15.49	18.69	20.52	9.29 ± 2.81	5.05	6.08	7.25	8.86	10.87	13.06	15.76	17.58
45 to < 65	10.23 ± 2.93	5.68	6.83	8.12	9.83	11.87	14.22	17.12	18.71	8.27 ± 2.39	4.46	5.47	6.53	7.98	9.67	11.48	13.76	15.04
65 to ≤ 96	8.07 ± 2.58	4.06	5.08	6.20	7.72	9.54	11.53	14.22	15.50	5.99 ± 2.13	2.80	3.54	4.42	5.67	7.22	8.91	10.96	12.17
	(L/kg-min)[b]																	
5 to < 7	0.263 ± 0.061	0.163	0.191	0.219	0.257	0.300	0.343	0.398	0.435	0.254 ± 0.059	0.157	0.184	0.212	0.248	0.290	0.334	0.386	0.414
7 to < 10	0.248 ± 0.072	0.137	0.165	0.196	0.238	0.289	0.345	0.415	0.464	0.231 ± 0.058	0.138	0.161	0.189	0.224	0.266	0.307	0.361	0.392
10 to < 16.5	0.241 ± 0.096	0.106	0.136	0.170	0.223	0.292	0.366	0.477	0.553	0.193 ± 0.068	0.093	0.116	0.143	0.183	0.229	0.285	0.355	0.395
16.5 to < 25	0.178 ± 0.048	0.103	0.122	0.143	0.172	0.206	0.244	0.290	0.312	0.173 ± 0.044	0.104	0.122	0.141	0.168	0.199	0.233	0.274	0.299
25 to < 35	0.162 ± 0.042	0.097	0.114	0.132	0.156	0.187	0.218	0.259	0.284	0.161 ± 0.044	0.092	0.110	0.129	0.155	0.186	0.219	0.261	0.285
35 to < 45	0.160 ± 0.049	0.086	0.104	0.125	0.152	0.188	0.225	0.273	0.300	0.159 ± 0.050	0.084	0.103	0.123	0.151	0.186	0.226	0.273	0.305
45 to < 65	0.144 ± 0.043	0.077	0.094	0.112	0.138	0.168	0.201	0.246	0.274	0.141 ± 0.042	0.075	0.092	0.111	0.136	0.166	0.198	0.237	0.266
65 to ≤ 96	0.119 ± 0.040	0.059	0.074	0.091	0.114	0.141	0.172	0.216	0.237	0.106 ± 0.040	0.047	0.061	0.077	0.100	0.128	0.160	0.200	0.221
	(L/m^2-min)[b]																	
5 to < 7	6.56 ± 1.44	4.15	4.80	5.52	6.43	7.45	8.47	9.73	10.51	6.32 ± 1.36	4.02	4.65	5.33	6.20	7.16	8.14	9.33	10.09
7 to < 10	6.70 ± 1.78	3.90	4.62	5.40	6.48	7.74	9.08	10.72	11.86	6.31 ± 1.45	3.92	4.57	5.26	6.16	7.20	8.29	9.51	10.31
10 to < 16.5	7.45 ± 2.68	3.54	4.43	5.48	7.03	8.95	11.04	13.82	15.53	6.07 ± 1.96	3.09	3.81	4.63	5.78	7.19	8.68	10.70	11.92
16.5 to < 25	6.71 ± 1.76	3.88	4.66	5.43	6.47	7.75	9.05	10.73	11.63	6.19 ± 1.51	3.77	4.42	5.09	6.02	7.10	8.23	9.54	10.46
25 to < 35	6.14 ± 1.53	3.73	4.35	5.03	5.94	7.05	8.15	9.66	10.57	5.72 ± 1.47	3.30	3.99	4.66	5.56	6.58	7.67	9.03	9.89
35 to < 45	6.03 ± 1.79	3.31	3.97	4.73	5.76	7.06	8.42	10.25	11.23	5.67 ± 1.73	3.02	3.69	4.41	5.41	6.64	7.99	9.65	10.68
45 to < 65	5.49 ± 1.61	3.02	3.63	4.32	5.27	6.39	7.63	9.30	10.20	5.07 ± 1.48	2.71	3.34	4	4.89	5.96	7.05	8.51	9.35
65 to ≤ 96	4.46 ± 1.45	2.22	2.79	3.42	4.25	5.27	6.40	7.92	8.75	3.76 ± 1.37	1.73	2.19	2.76	3.56	4.54	5.6	6.96	7.74

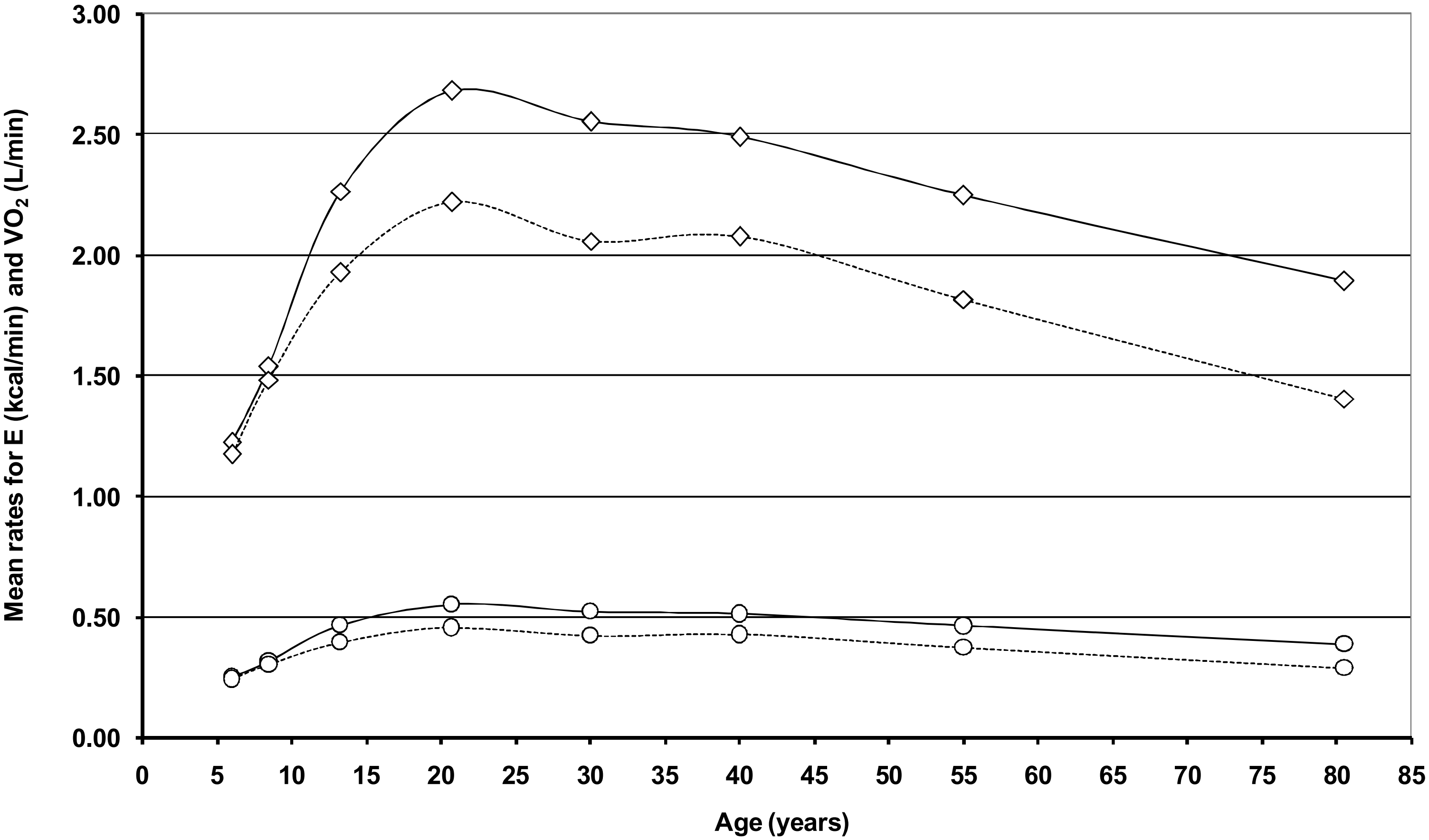
[a]VAα =[(TDEE-BEE)/((24-Sld) x 60) + (BEE+ECG)/1440] x H_Px VQα x (1-VDphysα/VTα), where VDphysα/VTα = ratio of the physiological dead space to the tidal volume, H_P = oxygen uptake factor and VQα = ventilatory equivalent. Values for VDphysα/VTα (unitless) are given in Table 2. TDEE, BEE, ECG and Sld are defined in Table 3. [b]VAα (L/min) were divided by body weights (Bw) and body surface areas (BSA) in order to obtain values expressed in L/kg-min and L/m^2-min respectively. [a, b]Values for TDEE, BEE, ECG (kcal/day), Sld (hours/day), Bw (kg), BSA (m^2), H_P (0.2059 ± 0.0019 L of O_2/kcal) and VQα (unitless) are reported in Brochu *et al.* (2010). S.D.= standard deviation.

Table 8 Distribution percentiles of ventilation-perfusion ratios for aggregate daytime activities of normal-weight individuals aged 5 to 96 years

Age group for both genders (years)	Ventilation-perfusion ratios[a] (L of alveolar air/L of blood)								
	Mean ± S.D.	Percentiles							
		2.5nd	10th	25th	50th	75th	90th	97.5th	99th
5 to < 7	1.49 ± 0.12	1.26	1.34	1.40	1.49	1.57	1.64	1.73	1.78
7 to < 10	1.49 ± 0.12	1.26	1.34	1.40	1.49	1.57	1.64	1.73	1.78
10 to < 16.5	1.53 ± 0.24	1.12	1.24	1.37	1.51	1.68	1.84	2.05	2.16
16.5 to < 25	1.36 ± 0.28	0.91	1.03	1.16	1.33	1.52	1.72	1.98	2.14
25 to < 35	1.35 ± 0.22	0.98	1.09	1.20	1.34	1.49	1.63	1.82	1.93
35 to < 45	1.34 ± 0.36	0.76	0.92	1.08	1.29	1.54	1.82	2.16	2.40
45 to < 65	1.31 ± 0.29	0.83	0.97	1.10	1.27	1.48	1.70	1.96	2.11
65 to ≤ 96	1.22 ± 0.27	0.78	0.91	1.03	1.19	1.38	1.58	1.83	1.98

[a]VAα/Qα. Values for Qα (L of blood/min) and VAα (L of alveolar air/min) are given in Tables 6 and 7 respectively.
S.D.=standard deviation.

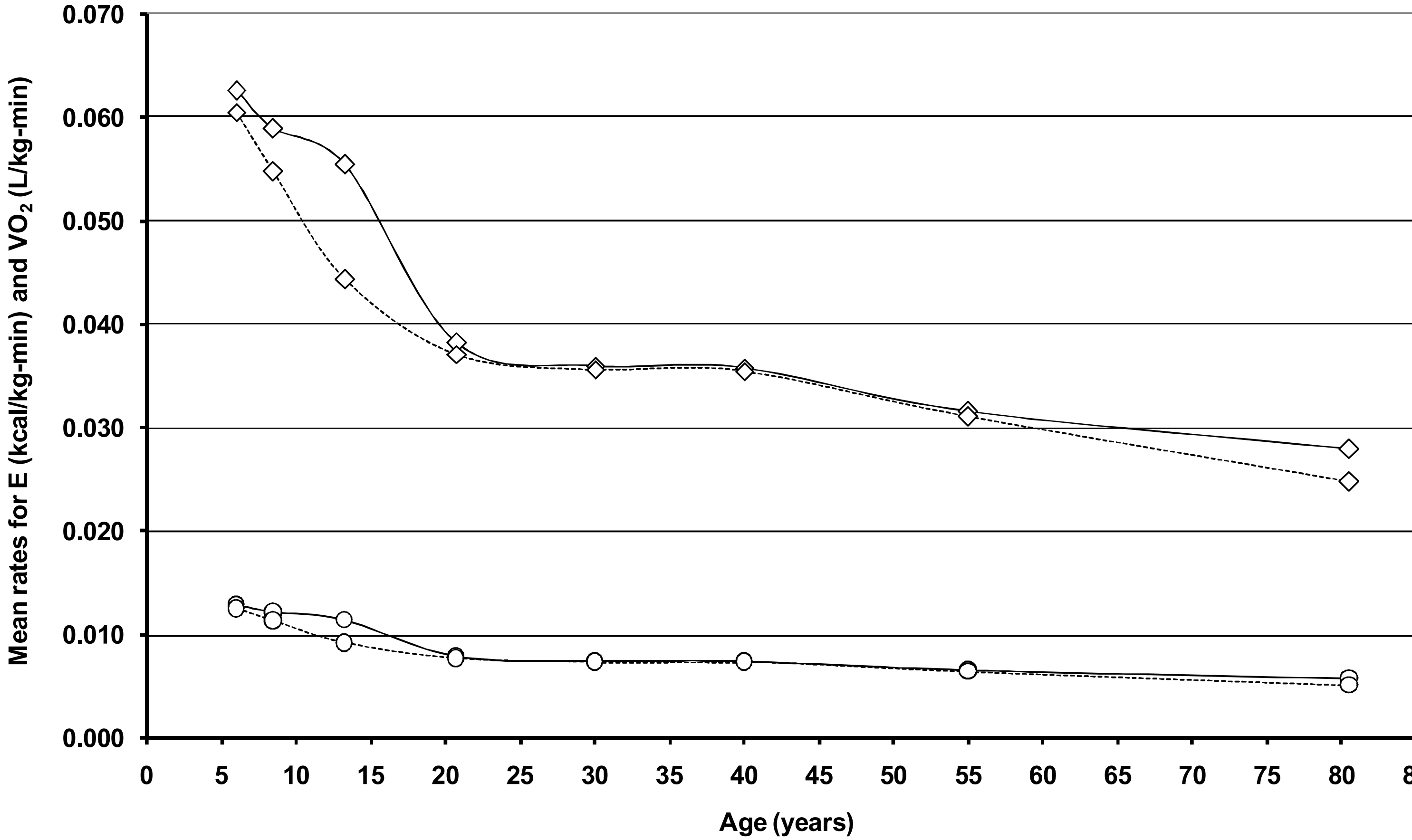
Figure 1 Mean minute energy expenditure (kcal/min) and oxygen consumption rates (L/min) for aggregate daytime activities of normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 3 and 4.
E = minute energy expenditure rate; VO_2 = oxygen consumption rate; males = solid line; females = dotted line.

—◇— E —○— VO_2

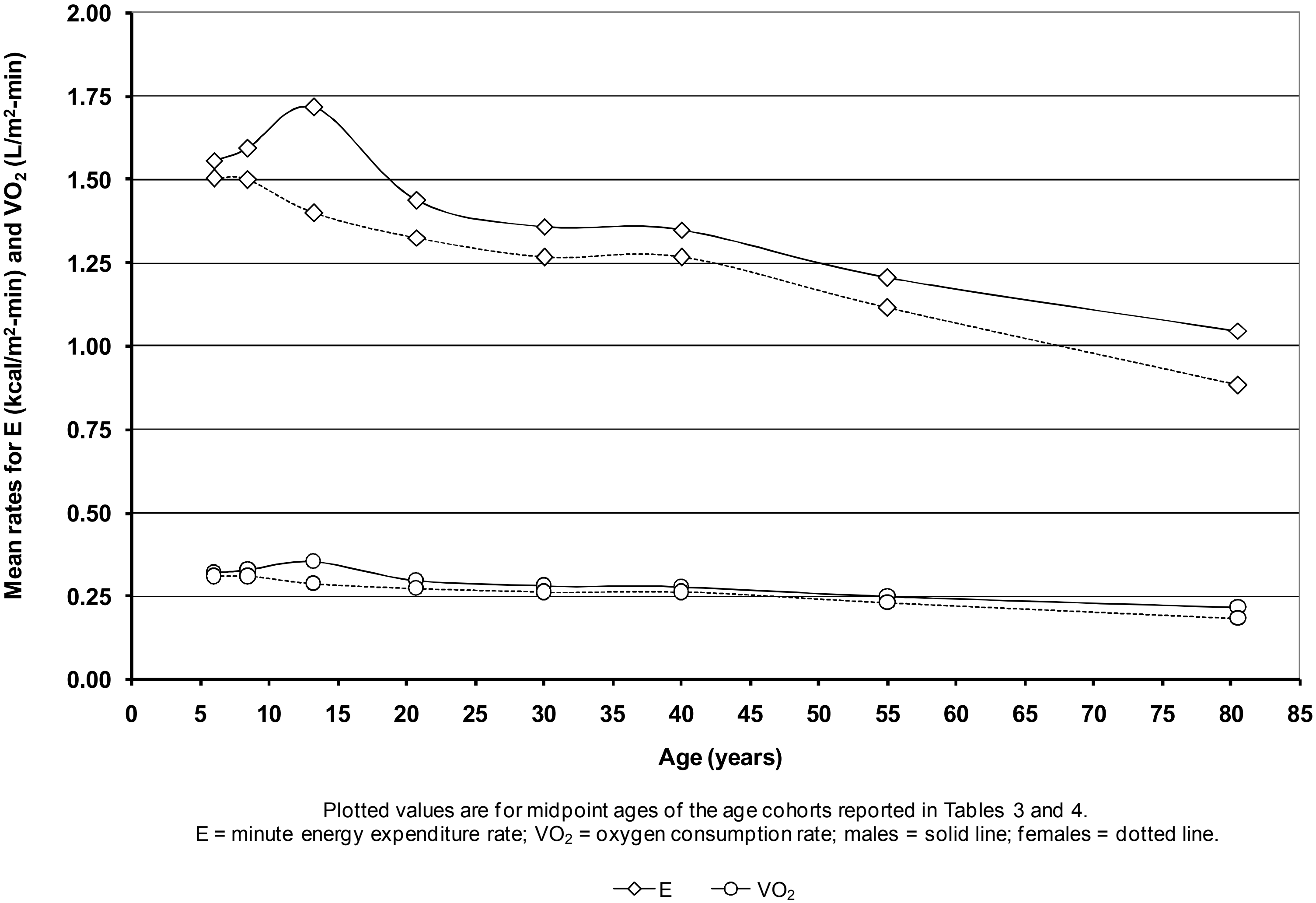
Figure 2 Mean minute energy expenditure (kcal/kg-min) and oxygen consumption rates (L/kg-min) for aggregate daytime activities of normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 3 and 4.
E = minute energy expenditure rate; VO_2 = oxygen consumption rate; males = solid line; females = dotted line.

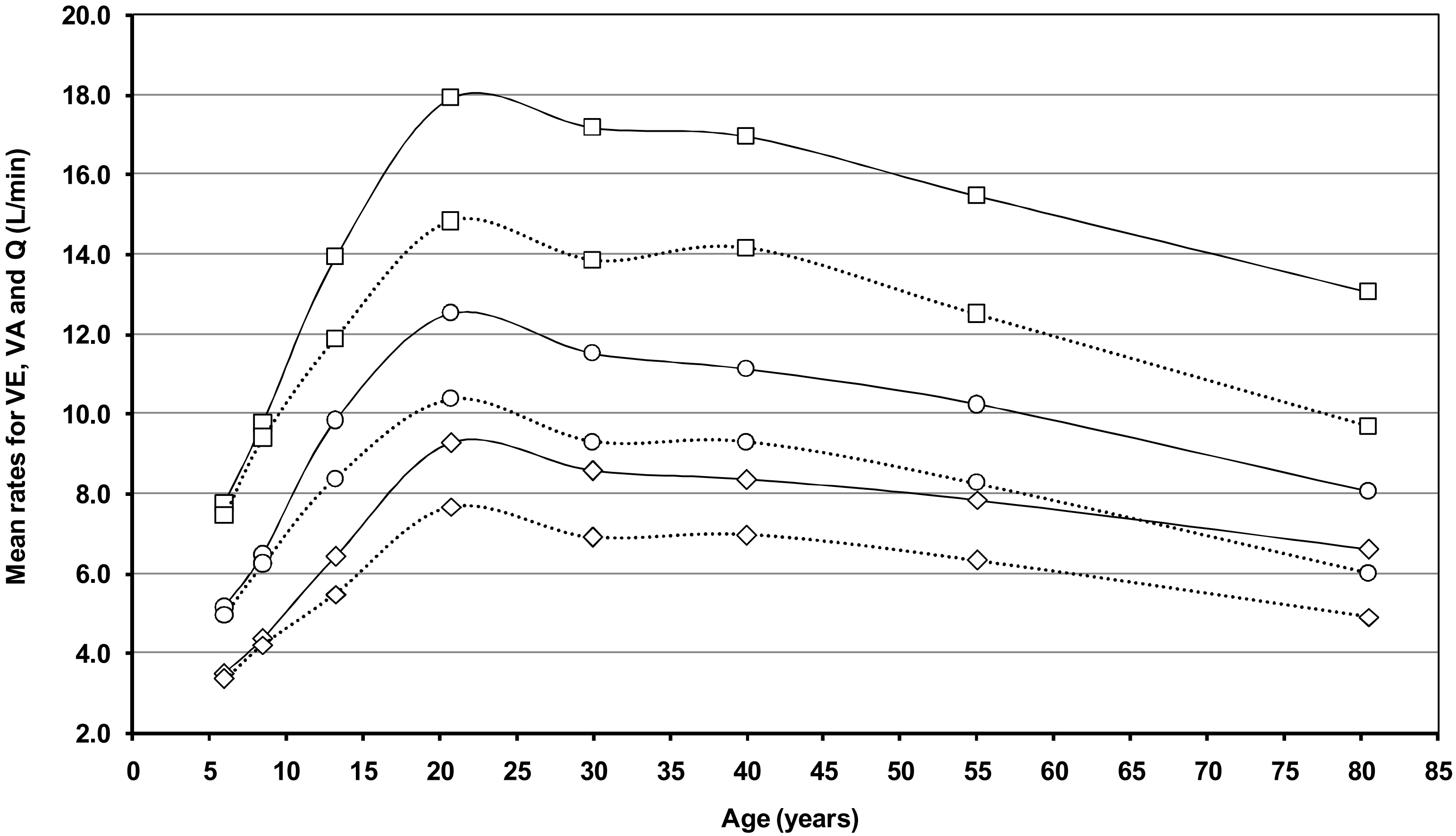
E VO_2

Figure 3 Mean minute energy expenditure (kcal/m²-min) and oxygen consumption rates (L/m²-min) for aggregate daytime activities of normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 3 and 4.
E = minute energy expenditure rate; VO_2 = oxygen consumption rate; males = solid line; females = dotted line.

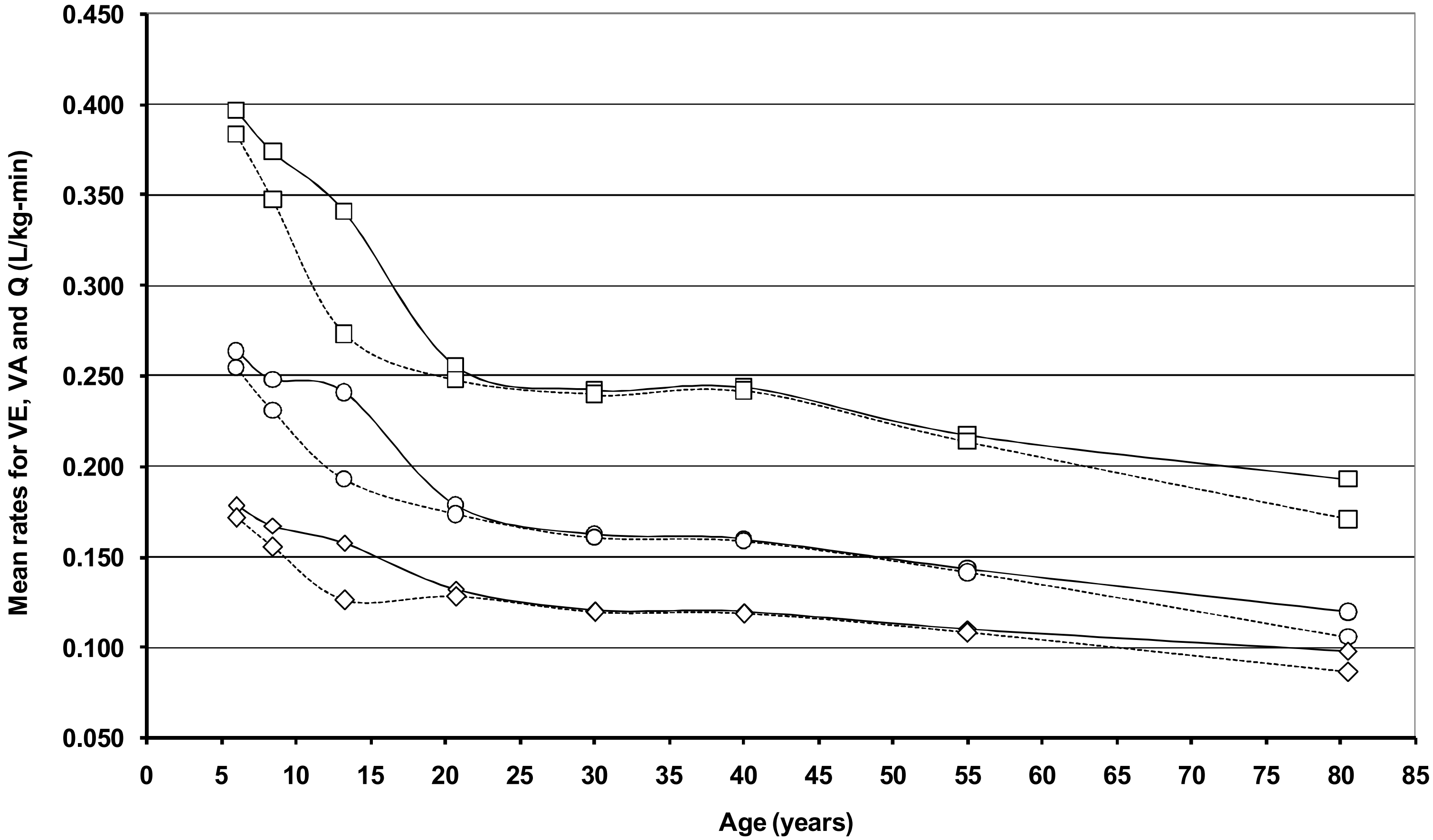
Figure 4 Mean minute ventilation rates, alveolar ventilation rates and cardiac outputs (L/min) for aggregate daytime activities of normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 5 to 7.
VE = minute ventilation rate; VA = alveolar ventilation rate; Q = cardiac output; males = solid line; females = dotted line.

—□— VE —○— VA —◇— Q

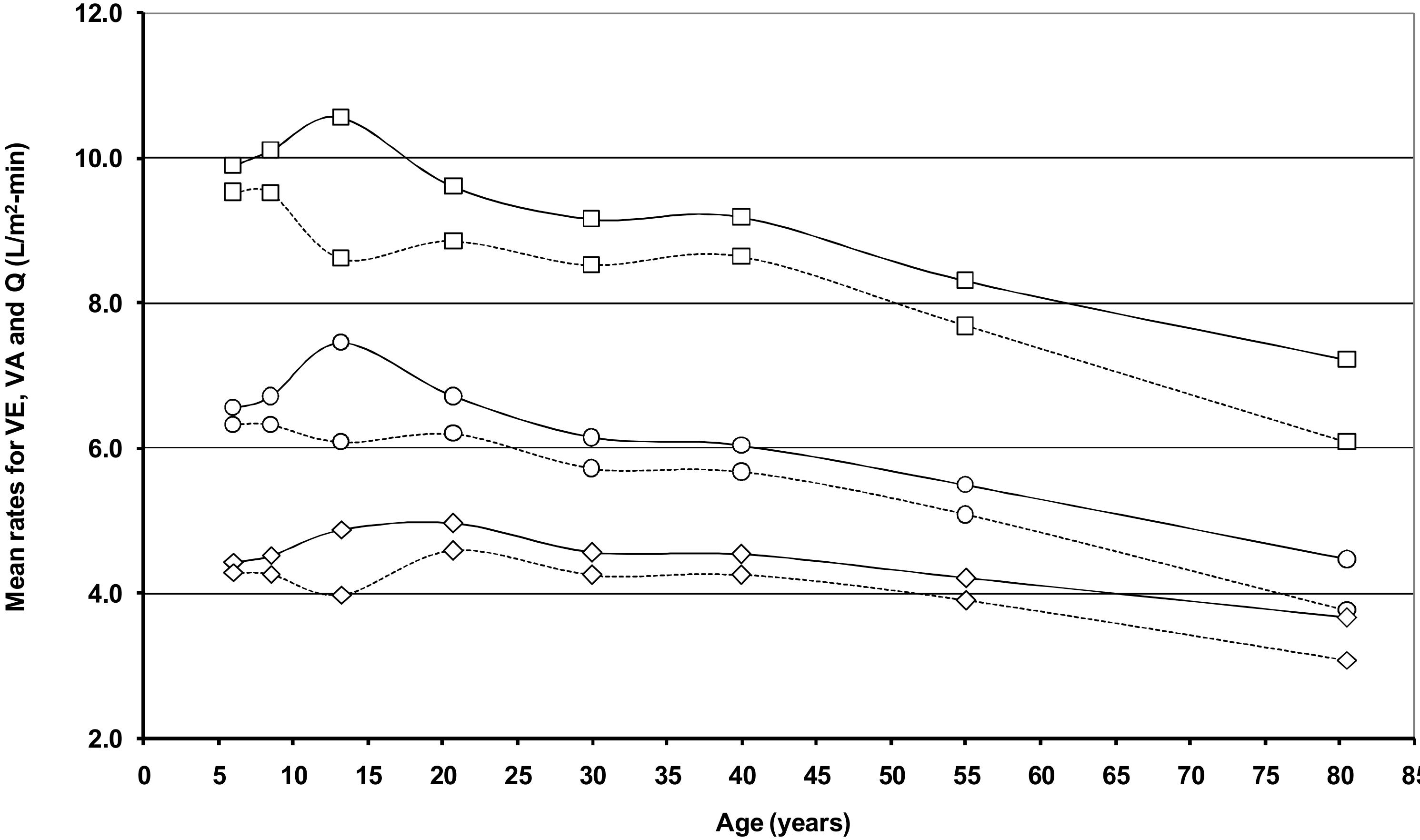
Figure 5 Mean minute ventilation rates, alveolar ventilation rates and cardiac outputs (L/kg-min) for aggregate daytime activities of normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 5 to 7.
VE = minute ventilation rate; VA = alveolar ventilation rate; Q = cardiac output; males = solid line; females = dotted line.

—□— VE —○— VA ---◇--- Q

Figure 6 Mean minute ventilation rates, alveolar ventilation rates and cardiac outputs (L/m²-min) for aggregate daytime activities of normal-weight males and females as a function of age



Plotted values are for midpoint ages of the age cohorts reported in Tables 5 to 7.
VE = minute ventilation rate; VA =alveolar ventilation rate; Q = cardiac output; males = solid line; females = dotted line.

—□— VE —○— VA ---◇--- Q

CHAPITRE SIXIEME :

6 DISCUSSION ET CONCLUSION

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Dans cette thèse, nous avons utilisé une approche originale pour la mesure du taux quotidien d'inhalation et celle des taux de ventilation minute, de la ventilation alvéolaire et du débit cardiaque chez l'humain. L'essentiel de l'introduction de la thèse est tiré de Brochu *et al.* (2006c). Nous y révisons de façon critique la littérature portant sur les approches traditionnelles servant à estimer la valeur des taux quotidiens d'inhalation des individus en fonction de l'âge. Nous avons mis en lumière l'existence de biais et imprécisions propres à chacune des ces valeurs. Nous en sommes venus à la conclusion que les variations physiologiques, non seulement celles des processus respiratoires mais aussi celles des processus cardio-vasculaires, pouvaient être déterminées en utilisant des mesures de l'ensemble des dépenses énergétiques volontaires et involontaires tout au long de la journée. Ces dépenses énergétiques reflètent de façon fidèle l'oxygénation requise pour la conduite des activités quotidiennes.

Nous en sommes venus également à la conclusion que la mesure la plus précise des dépenses énergétiques quotidiennes chez des sujets qui vaquent librement à leurs occupations, sans aucune inhibition dans leur habitude de vie, et ce 24 heures par jour pendant plusieurs jours, peut s'effectuer à l'aide de la méthode du double marquage isotopique des molécules d'eau. C'est cette mesure qui, utilisée dans des équations appropriées, conduit à celle des paramètres physiologiques d'intérêt. La base de données qui nous a servi d'intrants aux mesures de dépenses énergétiques quotidiennes provient de la littérature scientifique. Il s'agit de celle portant sur les dépenses énergétiques quotidiennes de base mesurées par calorimétrie indirecte et celle portant sur les dépenses énergétiques quotidiennes totales résultant des mesures des taux d'élimination urinaire ou salivaire de doses ingérées de deutérium (^{2}H) et d'oxygène lourd-18 (^{18}O) par spectrométrie de masse chez des sujets en santé observés pendant des périodes de 7 à 21 jours. Les résultats spectrométriques mesurés chez divers groupes d'individus (356 à 2197) vaquant librement à leur occupation pendant des périodes globales de plus de 30 000, 6 000, 19 000 et 14 000 journées ont été utilisés dans les calculs des Articles I, II, III et IV respectivement. La précision moyenne de ces dépenses énergétiques de base et de ces dépenses énergétiques totales, qui sont systématiquement mesurées chez chaque sujet au même titre que le poids corporel, la taille et l'indice de masse corporelle, varie de +1 à +2 et de –1,0 à +3,3% respectivement. L'ensemble ces données nous a permis d'obtenir le profil énergétique des individus par groupe d'âge et par catégorie de poids corporels.

Les résultats de notre recherche sont présentés dans les articles I à IV. Nous avons d'abord établi des valeurs de taux quotidiens d'inhalation chez des individus âgés de 1 mois à 96 ans (Articles I et II). Ces taux, exprimés aussi bien en valeurs absolues qu'en valeurs relatives au poids corporel, ont été calculés en utilisant les mesures de dépenses énergétiques quotidiennes totales. Nous avons ainsi déterminé des taux quotidiens d'inhalation 1) chez des nouveau-nés âgés de 1 mois nourris au sein ou nourris à l'aide de préparations lactées commerciales, 2) chez des sujets de poids corporel normal âgés de 2,6 mois à 96 ans, 3) chez des sujets de poids supérieurs au poids normal âgés de 4 à 96 ans, 4) chez des adultes sous-alimentés ou anorexiques, 5) chez des athlètes, des explorateurs et des soldats (Article I). Nous avons également établi les valeurs de taux quotidiens d'inhalation durant les 9^{e}, 22^{e} et 36^{e} semaines de grossesse et les 2^{e}, 6^{e} et 27^{e} semaines de lactation chez des adolescentes et des femmes âgées de 11 à 55 ans de différentes catégories de poids corporels (Article II). Nous avons calculé les limites inférieures et supérieures des centiles des taux quotidiens d'inhalation pour tous les sujets des deux sexes âgés de 2,6 mois à 96 ans de différents poids corporels, ainsi que pour les adolescentes et les femmes en gestation et en lactation (Articles I et II).

Nous avons déterminé des paramètres relatifs aux caractéristiques physiologiques des populations étudiées : les coûts énergétiques pour la croissance de la naissance à l'âge adulte (Article I) et pour la gestation et la lactation (Article II), les valeurs de l'équivalent ventilatoire pour la grossesse et pour la lactation (Article II), ainsi que la valeur du volume d'oxygène consommé par unité de dépense d'énergie selon les diètes alimentaires des Canadiens (Article I).

Nous avons observé que les sujets de poids corporel normal inhalaient plus d'air par unité de poids corporel que leurs congénères de poids plus lourd (Articles I et II). Nous en avons tiré la conclusion que les évaluations du risque et les décisions en matière de gestion du risque devraient se baser, pour être prudentes, sur les centiles des sujets de poids corporel normal (Articles I et II). C'est pourquoi dans les articles III et IV, nous nous sommes limité à déterminer les valeurs d'une série de paramètres respiratoires et cardio-vasculaires seulement chez les sujets des deux sexes de poids corporel normal, et ce en utilisant conjointement les mesures des dépenses énergétiques quotidiennes de base et des dépenses énergétiques quotidiennes totales (Articles III et IV). Ceci nous a permis, dans l'Article III, de bonifier, par rapport à l'Article I, la précision des valeurs des taux quotidiens d'inhalation chez des sujets âgés de 2,6 mois à 96 ans. Cette bonification a été possible en déterminant et en combinant, pour la première fois dans le processus de calcul des taux quotidiens d'inhalation, les valeurs des moyennes et des écart-types des équivalents ventilatoires et des volumes d'oxygène consommé par unité de dépense d'énergie pendant la nuit (phase de jeûne), d'une part, avec celles pendant le jour (phase postprandiale), d'autre part. Les moyennes et écart-types de jour nous ont permis de déterminer les valeurs des taux de dépenses d'énergie par minute, des taux de consommation d'oxygène et des paramètres cardio-pulmonaires suivants, et ce pour l'ensemble des activités de la journée chez des individus âgés de 5 à 96 ans (Article IV): taux de ventilation minute, taux de ventilation alvéolaire, débit cardiaque et ratio de la ventilation-perfusion. Nous avons calculé les moyennes, les écart-types, ainsi que les distributions des centiles de tous ces paramètres respiratoires et cardio-vasculaires. Ces derniers ont été exprimés aussi bien en valeurs absolues qu'en valeurs relatives au poids corporel et à la surface corporelle, exception faites des ratios de la ventilation-perfusion (sans unité).

Nous avons établi les valeurs de l'équivalent ventilatoire pour les différents groupes d'âge de sujets au repos ou pour l'ensemble des activités de leur journée. Ces calculs ont été effectués en utilisant des données de la littérature, celles portant sur des mesures simultanées de taux de consommation d'oxygène et de ventilation minute. Nous avons établi les valeurs du volume d'oxygène consommé par unité de dépense d'énergie chez des sujets durant la phase postprandiale et, chez d'autres, durant la phase de jeûne. Nous avons calculé et analysé la fluctuation des valeurs postprandiales selon les diètes alimentaires typiques de 17 pays. Notre analyse a dépassé le stade connu d'exploitation des données alimentaires en exploitant, en plus, des séries de mesures publiées de taux de consommation d'oxygène et de production de bioxyde de carbone pour calculer les valeurs postprandiales, mais également celles pour la phase de jeûne. Tous ces calculs ont été effectués en utilisant un large éventail de données publiées dans la littérature, ceci afin de cerner la variabilité interindividuelle des données.

Nous avons établi des critères permettant de retenir, à partir de la littérature, les données utiles pour calculer les valeurs 1) des équivalents ventilatoires (taux de ventilation minute), 2) des volumes d'oxygène consommé par unité de dépense d'énergie (production de bioxyde de carbone), 3) des taux de ventilation alvéolaire (ratios de l'espace mort physiologique sur le volume courant), 4) des débits cardiaques (différence artérioveineuse en oxygène, ou fréquence et volume cardiaques). Les seules données retenues ont été celles mesurées chez des sujets en santé qui consommaient un taux d'oxygène d'environ 0,06 à 0,36 L/min au repos et 0,06 à 0,81 L/min lors d'effort. De plus, la concentration d'oxygène inhalé devait être de 21% et la pression barométrique devait se rapprocher de celle du niveau de la mer. Enfin, les données retenues pour la détermination des taux de ventilation alvéolaires et des débits cardiaques devaient avoir toutes été mesurées exclusivement chez des sujets en position verticale (assise ou debout).

Les taux d'oxygénation chez les sujets au repos (0,06 à 0,36 L/min) ont été déterminés pour chaque groupe d'âge en utilisant leurs dépenses énergétiques quotidiennes de base. En soustrayant ces dépenses énergétiques de base des dépenses énergétiques quotidiennes totales pour ces sujets, nous avons établi leurs taux de consommation d'oxygène durant l'ensemble de leurs activités de la journée (0,06 à 0,81 L/min). Ces deux types de taux de consommation d'oxygène pour chaque groupe d'âge, basés sur des données énergétiques de base et des données énergétiques totales mesurées chez des mêmes sujets, sont de première importance pour la sélection des données en vue du calcul des paramètres d'intérêt. Nous avons retracé dans la littérature plusieurs milliers de données mesurées lors de taux de consommation d'oxygène élevés obtenues chez des sujets exécutant des exercices modérément ou très exigeants, sous des conditions sub-anaérobie ou anaérobie (par exemple, marche rapide ou course sur un tapis roulant). Plusieurs des ces études portent d'ailleurs sur des mesures de données lors de taux de consommation maximale d'oxygène (VO_2Max) chez des sujets lors d'effort maximal. Les valeurs des VO_2Max varient de 0,86 à 2,62 L/min chez des enfants âgés de un à moins de 10 ans et de 1,50 à 5,63 L/min chez des individus âgés de 10 à 96 ans (Article IV). Nous avons retracé des taux d'oxygénation sous le seuil anaérobique pour des sujets des mêmes groupes d'âge variant de 0,54 à 0,70 et de 0,72 à 1,81 L/min respectivement. Nous avons constaté que ces mesures ponctuelles ont peu d'influence sur les valeurs quotidiennes, les taux d'oxygénation durant l'ensemble des activités de la journée des enfants âgés de moins de 10 ans et des sujets de 10 à 96 ans variant seulement de 0,06 à 0,55 et de 0,16 à 0,81 L/min respectivement (Article IV). Nous en sommes donc venus à la conclusion que l'exécution d'efforts en condition sub-anaérobie et anaérobie représentait, dans la réalité de tous les jours, des événements suffisamment rares et de durées suffisamment courtes, faisant en sorte qu'ils étaient dilués dans le large processus d'oxygénation aérobie, lequel est effectif de façon continue durant l'ensemble des activités de la journée. Ces critères de sélection nous ont permis d'éliminer plus de 20 000 données qui auraient biaisé les valeurs des paramètres respiratoires et cardio-vasculaires.

Les mesures simultanées d'échange gazeux d'oxygène et de bioxyde de carbone chez des sujets à jeun nous ont permis de conclure que les volumes d'oxygène consommé par unité de dépense d'énergie lors de la phase de jeûne et de la phase postprandiale ne varient pas en fonction de la position des individus. Nous avons observé que les valeurs postprandiales ne varient pas, non plus, en fonction de l'âge, ni du sexe, ni des indices de masses corporelles lorsque la diète alimentaire est identique : le changement de diète alimentaire demeure le seul paramètre déterminant. Par contre, nous avons calculé que l'utilisation de l'une ou l'autre des valeurs extrêmes qui ont été calculées selon les diètes alimentaires des Vietnamiens (0,203 L d'O_2/kcal, n=17 763) d'abord et des Américains (0,208 L d'O_2/kcal, n=77 278) ensuite, au lieu de la valeur retenue de 0,206 L d'O_2/kcal, aurait affecté la valeur des taux quotidiens d'inhalation par seulement -1,2 à -0,7% et de +0,5 à +0,9 % respectivement. Ceci s'explique par le fait que la valeur de la phase de jeûne (0,206 L d'O_2/kcal) de nuit, se situe, comme la valeur postprandiale retenue de jour (0,206 L d'O_2/kcal), environ à mi-chemin entre les deux valeurs extrêmes des Vietnamiens (0,203 L d'O_2/kcal) et des Américains (0,208 L d'O_2/kcal).

Comparativement aux Articles I et II, nous avons utilisé, dans le processus de calcul des paramètres respiratoires et cardio-vasculaires pour les Articles III et IV, des valeurs de périodes de sommeil des sujets. Nous avons retenu les données d'études portant sur de larges groupes d'individus afin d'obtenir la variabilité interindividuelle lors des périodes de sommeil par groupe d'âge. Nous avons vérifié si des périodes de sommeil plus courtes chez des individus souffrant d'embonpoint ou d'obésité pouvaient biaiser les valeurs des paramètres respiratoires et cardio-vasculaires pour des sujets de poids corporel normal en développant une procédure de calcul basée sur les pires scénarios. Nous avons ainsi déterminé, en utilisant des scénarios extrêmes, que les périodes de sommeil plus courtes des sujets de poids corporels supérieurs au poids normal auraient une influence négligeable sur les valeurs des taux quotidiens d'inhalation (-0,17 à -0,03%), celles des taux de consommation d'oxygène, de ventilation minute, de ventilation alvéolaire et de débit cardiaque (-1,2 à -0,5%) et que les valeurs des ratios de ventilation-perfusion ne seraient pas altérées.

Comparaison des résultats de la recherche

On ne retrouve pas dans la littérature des taux quotidiens d'inhalation estimés pour des individus classifiés par catégorie de poids (selon les indices de masse corporelle), ni pour les femmes en gestation ou en lactation. De plus, les travaux de Brochu *et al.* (2006c) ont démontré que les approches connues pour estimer des taux quotidiens d'inhalation étaient biaisées et que des moyennes et des centiles de ces taux étaient erronés par -47 à +121%. Ces pourcentages d'erreurs s'ajoutaient aux imprécisions associées aux mesures spectrométriques du double marquage des molécules d'eau (-1,0 à +3,3%). Ce qui précède explique les différences que nous observons entre les moyennes et les centiles des taux quotidiens d'inhalation déterminés dans les Articles I et III par rapport à ceux de la littérature. Par exemple, les 5^{e} centiles de l'USEPA (2006) pour des garçons (0,964 m^3/kg-jour) et des filles (0,975 m^3/kg-jour) âgés de 1 an sont supérieurs aux 99^{e} centiles de l'Article III (0,787 et 0,785 m^3/kg-jour respectivement) pour des garçons et des filles de poids corporel normal âgés de 1 à moins de 2 ans. À l'inverse, les taux moyens de 2,14 m^3/jour de Allan et Richardson (1998) et de 2,18 m^3/jour de Allan *et al.* (2008) estimés pour des enfants âgés de moins de 7 mois sont inférieurs au taux quotidien de 3,68 m^3/jour de l'Article III pour des enfants âgés de 2,6 à moins de 6 mois, et même plus faible que celui de 3,09 m^3/jour nécessaire pour leur besoin métabolique de base.

Nous avons observé que les valeurs exprimées par unité de poids corporel des taux quotidiens d'inhalation (Articles I, III) et des paramètres cardio-vasculaires (Article IV) étaient tous plus élevées chez les enfants que chez les adultes. Ces résultats concordent avec les données connues de la physiologie cardio-vasculaire. Les apports alimentaires en énergie et les dépenses d'énergie exprimés par unité de poids corporel des enfants sont supérieurs à ceux des adultes (Durnin et Passmore 1967; Layton 1993). Le nombre d'alvéoles par unité de poids corporel et par unité de surface corporel est plus élevé chez les enfants que chez les adultes (Artile IV : Dunnill 1962; Davies et Reid 1970; Angus et Thurlbeck 1972). Les concentrations sanguines d'hémoglobine sont plus faibles chez les enfants âgés d'environ 3 mois et elles augmentent en fonction de l'âge jusqu'à l'état adulte (Motoyama *et al.* 1990). Les teneurs sanguines en diphospho-2, 3 glycérate sont plus élevées chez les enfants que chez les adultes et surtout, dès la naissance jusqu'à l'âge de 8 ans (Motoyama *et al.* 1990). Tel que prévu par la science, nous avons donc observé un taux d'oxygénation plus élevé (en L/kg-min) associé à une dépense d'énergie plus élevée (en kcal/kg-min) chez les enfants (Article IV). Nous avons constaté que pour palier à leurs handicaps biochimiques et en réponse à cette demande plus élevée en oxygène, leurs taux de ventilation alvéolaire (en L/kg-min) étaient supérieurs à ceux des adultes afin de maintenir une concentration sanguine adéquate en oxygène. Nous avons constaté que ces niveaux supérieurs de ventilation alvéolaire étaient assurés par des taux de ventilation minute (en L/kg-min) et des taux quotidiens d'inhalation (en m^3/kg-jour) également plus élevés, au même titre que les débits cardiaques (en L/kg-min) afin de maximiser le transport de l'oxygène à tous leurs tissus (Articles I, III et IV).

Dans l'Article IV, les taux de ventilation alvéolaire (VA) ont été calculés à partir des taux de ventilation minute. Ces derniers ont été déterminés à partir des taux de consommation d'oxygène qui eux, ont été utilisés pour calculer les débits cardiaques (Q). Nous avons observé que les valeurs de la majorité des centiles des ratios de la ventilation-perfusion (c.-à-d. des ratios VA/Q), ou des taux de ventilation minute (utilisés pour calculer VA), des taux de ventilation alvéolaire (VA) et des débits cardiaques (Q) de l'Article IV concordaient très bien avec les valeurs de la littérature, lorsqu'on prenait notamment en compte les différences de taux de consommation d'oxygène (références citées dans l'Article IV). Les efforts plus exigeants se traduisent par des taux de consommation d'oxygène (VO_2) et des paramètres cardio-pulmonaires (dont les ratios VA/Q) plus élevés, lorsque les sujets concernés ont environ le même âge et le même niveau d'entraînement. Par exemple, l'écart entre le 2,5^e et le 99^e centile des ratios VA/Q variant de 1,12 à 2,16 pour des garçons et des filles âgés de 10 à moins de 16,5 ans pour des VO_2 de 0,229 à 0,806 L/min (Article IV) correspond très bien aux ratios de la littérature variant de 1,07 à 2,49 mesurés chez des garçons âgés de 11 à 13 ans (n=9) durant des efforts nécessitant une demande de VO_2 variant de 0,24 à 1,14 L/min. La différence entre ces ratios maximaux s'explique majoritairement par des efforts plus exigeants durant la mesure du ratio de 2,49 de la littérature, confirmés par un VO_2 plus élevé de 1,14 L/min comparativement au VO_2 plus faible de 0,806 L/min pour le ratio de 2,16. L'écart entre le 2,5^e et le 10^e centile des ratios VA/Q variant de 0,78 à 1,09 pour des sujets âgés de 16,5 à moins de 96 ans sont compatibles avec les valeurs individuelles et moyennes publiées pour les ratios VA/Q variant de 0,58 à 1,13 (n=20) et de 0,74 ± 0,09 à 0,87± 0,28 (n=77) pour des adultes au repos selon des taux d'oxygénation typiques de 0,236 à 0,454 L/min.

L'écart entre le 2,5^{e} et le 99^{e} centile des ratios VA/Q des individus âgés de 16,5 à moins de 25 ans varie de 0,91 à 2,14, tandis que celui entre le 10^{e} et le 99^{e} centile des ratios des sujets âgés de 35 à moins de 45 ans varie de 0,92 à 2,40 pour des taux de ventilation minute (calculés selon les VO_2) variant de 9,22 à 30,41 et de 9,28 à 31,39 L/min respectivement (Article IV). Ces ratios sont du même ordre que ceux variant de 0,90 à 2,45 que nous avons calculés à partir des taux de ventilation alvéolaire (VA) et des débits cardiaques (Q) qui ont été mesurés chez des femmes âgées de 20 à 30 ans (n=8) lors d'effort nécessitant des taux de ventilation minute compatibles avec ceux mentionnés, variant de 9 à 31 L/min. Ces 99^{e} centiles des ratios VA/Q de 2,14 et 2,40 (taux de ventilation minute de 30,41 et 31,39 L/min respectivement) sont cohérents par rapport au ratio VA/Q plus élevé de 2,61 que nous avons calculé selon les données publiées pour des hommes âgés de 20 à 30 ans (n=7) durant des efforts physiques plus exigeants nécessitant un taux de ventilation plus élevé de 38,2 L/min. Il en est de même lorsqu'on compare le 99^{e} centile du ratio VA/Q de 1,93 pour des sujets âgés de 25 à moins de 35 ans (VO_2 de 0,648 to 0,796 L/min) par rapport aux ratios VA/Q plus élevés variant de 2,00 à 2,01 calculés selon les mesures chez des femmes âgées de 23,6 à 30,2 ans (n=17) durant des VO_2 plus élevés (0,79 à 0,83 L/min).

Aucun ratio VA/Q n'est disponible dans la littérature pour des enfants plus jeunes, ni pour des adultes plus âgés. Par contre, des centiles des taux de ventilation minute (nécessaires pour calculer les VA), des taux de ventilation alvéolaire (VA) et des débits cardiaques (Q) de l'Article IV pour des sujets de ces âges correspondent bien aux rares données publiées. Par exemple, l'écart entre le 25^{e} et le 99^{e} centile des taux de ventilation minute (Article IV) des hommes et des femmes âgés de 45 à moins de 65 ans varie de 6,78 à 28,06 L/min

(VO_2 de 0,240 à 0,671 L/min), tandis que celui des hommes âgés de 65 à 96 ans varie de 4,52 to 25,16 L/min (VO_2 de 0,157 à 0,611 L/min). Ces taux concordent bien avec ceux de la littérature variant de 5,6 à 32,3 L/min (VO_2 de 0,236 à 0,797 L/min) chez des adultes âgés de 45 to 63 ans (n=40) et de 5,71 à 25,1 L/min (VO_2 de 0,167 à 0,673 L/min) chez des hommes âgés de 65 à 91 ans (n=29) respectivement. L'écart entre le 25^{e} et le 99^{e} centile des débits cardiaques des individus âgés de 45 à 96 ans variant de 3,89 à 11,65 L/min dans l'Article IV (VO_2 de 0,230 à 0,671 L/min) est en accord avec les valeurs publiées variant de 3,7 à 12,30 L/min (VO_2 de 0,202 à 0,47 L/min) pour des sujets âgés de 45 à 73 ans (n=48). Les mesures cardio-pulmonaires sont extrêmement rares chez les enfants âgés de moins de 10 ans. Néanmoins, nous avons observé que l'écart entre le 25^{e} et le 99^{e} centile des taux de ventilation alvéolaire (VA) de 5,26 à 8,63 L/min (VO_2 de 0,259 à 0,417 L/min) des enfants âgés de 7 à moins de 10 ans de l'Article IV était cohérent par rapport aux rares valeurs de la littérature variant de 5,03 à 9,03 L/min pour des enfants plus vieux âgés de 6 à 17 ans (n=56), lors de VO_2 relativement similaires variant de 0,262 à 0,389 L/min. Les 97,5^{e} centiles des débits cardiaques de 6,73 L/min des garçons et de 6,23 L/min des filles âgées de 7 à moins de 10 ans pour des VO_2 de 0,487 et 0,446 L/min respectivement (Article IV) sont aussi en accord avec les débits cardiaques de la littérature de 6,80 L/min chez des garçons (n=12) et 6,60 L/min chez des filles (n=12) âgés de 7 à 9 ans qui ont été mesurés lors de VO_2 de 0,55 et de 0,51 L/min respectivement.

Cette cohérence entre les valeurs des paramètres cardio-pulmonaires de l'Article IV (dont les ratios VA/Q) et celles de la littérature valide les processus de calculs et les valeurs des taux de ventilation alvéolaire (VA) et des débits cardiaques (Q), et donc l'ordre de grandeur des données qui ont été nécessaires pour calculer les taux de ventilation alvéolaire d'une part (taux de ventilation minute, ratios de l'espace mort physiologique sur le volume courant) et les débits cardiaques d'autre part (taux de consommation d'oxygène, différences artérioveineuses en oxygène), de même que les paramètres complémentaires (volumes d'oxygène consommé par unité de dépense d'énergie, équivalents ventilatoires et périodes de sommeil). L'ordre de grandeur des valeurs des dépenses énergétiques de base et totales, ainsi que des coûts énergétiques pour la croissance qui ont été utilisés pour déterminer ces paramètres de l'Article IV et également les taux quotidiens d'inhalation des sujets âgés de 5 à 96 ans dans l'Article III se retrouve du même coup validé.

Les erreurs moyennes associées aux volumes d'oxygène consommé par unité de dépense d'énergie (-2 à -1%), aux dépenses énergétiques de bases (+1 à +2%), aux coûts énergétiques pour la croissance et aux dépenses énergétiques totales (–1,0 à +3,3%) ont été calculées comme pouvant affecter la précision moyenne des taux quotidiens d'inhalation de l'Article III par -3,0 à +2,3% et des paramètres cardio-vasculaires de l'Article IV par -2,8 à +4,0%. À cet égard, soulignons que la procédure que nous avons développée selon les données publiées en rapport au double marquage des molécules d'eau et publiée en 2006 (Articles I, II et Brochu *et al.* 2006c) a également été évaluée par le Centre National d'Évaluation Environnementale des États-Unis (NCEA 2007) et l'Institut National de Santé Publique et de l'Environnement des Pays-Bas (Van Engelen *et al.* 2007) comme permettant de calculer les taux quotidiens d'inhalation les plus précis de la littérature actuelle.

Contribution des résultats à l'avancement des connaissances

Les taux quotidiens d'inhalation chez les nouveau-nés et chez les sujets de différentes catégories de poids corporels âgés de 2,6 mois à 96 ans n'avaient jamais été publiés à ce jour. On ne retrouvait pas non plus dans la littérature des valeurs de taux quotidiens d'inhalation pour les adolescentes et les femmes enceintes et celles en lactation. Les taux publiés dans les Articles I, II et dans Brochu *et al.* (2006c) ont donc comblé un besoin scientifique. Il en sera de même lors la publication des taux quotidiens d'inhalation de l'Article III. D'ailleurs, durant la rédaction de la présente thèse, l'expertise et les taux quotidiens d'inhalation des Articles I, II et de Brochu *et al.* (2006c) ont été cités et/ou utilisés dans plusieurs études en évaluation et/ou en gestion du risque toxicologique chez l'humain, notamment par l'Institut National de Santé Publique du Québec, Santé Canada, l'Agence de Protection Environnementale des États-Unis et par des organismes de la Communauté Européenne (information plus détaillée et références citées en postface).

Les moyennes et les écart-types des équivalents ventilatoires pour les différents groupes d'âge des sujets, ainsi que les moyennes et les écart-types des volumes d'oxygène consommé par unité de dépense d'énergie durant les phases postprandiale et de jeûne que nous avons déterminés (Article III) comblent également des lacunes signalées par plusieurs chercheurs (NCEA 2006, Arcus-Arth et Blaisdell, 2007; NCEA 2009). Ces données nous ont permis de développer des équations physiologiques originales, faisant le lien physiologique entre les dépenses d'énergie et les paramètres respiratoires et cardiovasculaires (Articles III et IV). Le NCEA (2009) a récemment annoncé que l'estimation des taux de ventilation alvéolaire faisait partie d'activités de recherche à venir. Dans la présente thèse, nous avons déterminé non seulement les valeurs des taux de ventilation alvéolaire, mais aussi celles d'une série de paramètres respiratoires et cardio-vasculaires pour l'ensemble des activités de la journée de sujets âgés de 5 à 96 ans : dépenses d'énergie par minute, taux de consommation d'oxygène, taux de ventilation minute, ratios de l'espace mort physiologique sur le volume courant, différences artérioveineuses en oxygène, débits cardiaques et ratios de la ventilation-perfusion (Article IV). Ces données s'ajoutent à celles portant sur les taux quotidiens d'inhalation calculés pour les mêmes sujets et pour les mêmes groupes d'âge (Article III).

Les valeurs des taux quotidiens d'inhalation et des paramètres cardio-pulmonaires des Articles I à IV sont basées sur des mesures précises obtenues par le double marquage isotopique des molécules d'eau, lesquelles n'ont jamais été exploitées en toxicologie ni en gestion et en analyse du risque (Bluck 2008). De plus, ces valeurs découlant des Articles I à IV comblent d'importantes lacunes au niveau des connaissances actuelles. Par exemple, nous avons observé que les moyennes et les centiles des taux quotidiens d'inhalation (en m^3/kg-jour) sont plus élevés chez les enfants que chez les adultes, plus élevés chez les individus de poids légers que chez leurs congénères de poids plus lourds, plus élevés chez les sujets de sexe masculin que chez ceux de sexe féminin (Articles I et III). Nous avons constaté que les adolescentes et les femmes enceintes et celles qui allaitent leur bébé inhalent plus d'air par jour (en m^3/jour) et par unité de poids corporel (en m^3/kg-jour), donc plus de polluants, que leurs homologues masculins aux mêmes concentrations d'exposition, exception fait de certains athlètes, soldats et explorateurs (Articles I, II et III). Par ailleurs, les nouveau-nés et les enfants de poids corporel normal âgés de 2,6 mois à moins de 10 ans inhalent plus d'air par unité de poids corporel (en m^3/kg-jour), donc plus de contaminants que ces adolescentes et ces femmes, même si les équivalents ventilatoires (34,2 à 36,8) de ces dernières sont plus élevés que ceux des enfants (30,2 et 30,8) pour des volumes d'oxygène consommé par unité de dépense d'énergie similaires (Articles II, III).

La plupart des moyennes et des centiles des paramètres cardio-pulmonaires calculés pour l'ensemble de la journée des individus de poids corporel normal sont également plus élevés chez les enfants de 5 à moins de 16,5 ans que chez les sujets plus âgés (Article IV). Nous en sommes venus à la conclusion que les apports inhalés (en µg/kg-min) et absorbés (en µg/L de sang) en polluants liposolubles seraient fréquemment plus élevés chez ces enfants que chez les sujets plus âgés pour des niveaux d'exposition et des comportements des xénobiotiques identiques (dont les taux d'absorption) peu importe l'âge des individus.

Les valeurs des taux quotidiens d'inhalation et des paramètres cardio-pulmonaires des Articles I à IV pourront servir de base à des calculs reflétant de façon fidèle la réalité biologique chez l'humain : 1) apports de contaminants inhalés (en µg/kg) lors de certaines études épidémiologiques destinées à évaluer le risque, 2) $NOAEL_H$ à partir des $NOAEL_A$ chez l'animal (en µg/m^3) en vue de la gestion du risque et 3) doses internes de xénobiotiques environnementaux et de métabolites (en µg/L de sang) lors d'études pharmacocinétiques à base physiologique. Elles permettront le développement de nouvelles procédures en analyse et en gestion du risque pour mieux protéger les populations contre les polluants de l'air extérieur et de l'air intérieur, dont les populations susceptibles suivantes : les enfants, les adolescentes et les femmes enceintes et celles en lactation. À titre d'exemple, les valeurs des $NOAEL_{[HEC]}$ de l'EPA (en µg/m^3) basées sur le taux de ventilation alvéolaire approximatif de 9,7 L/min et la surface pulmonaire de 54 m^2, pour des xénobiotiques qui ne s'accumulent pas significativement dans le sang et qui ont des effets au niveau pulmonaire, seraient 2 fois plus faibles en utilisant le taux moyen de ventilation alvéolaire de 11,52 L/min (Article IV) et la surface pulmonaire de 139 m^2 (USEPA 1994) pour les hommes âgés de 25 à moins de 35 ans. L'utilisation de ce taux alvéolaire (11,52 L/min) se traduirait par des valeurs calculées de RfCs par l'EPA proportionnellement 2 fois plus sévères, les valeurs retenues pour les facteurs de sécurité n'étant pas affectées par ailleurs. Les valeurs des $NOAEL_H$ de Santé Canada pourraient également être abaissées par un facteur de 2,6 suite à l'utilisation du 99^e centile le plus élevé du taux d'inhalation chez les enfants, soit de 1,138 m^3/kg-jour (Article III), comparativement au taux moyen actuel (0,444 m^3/kg-jour) retenu pour des enfants âgés de 5 à 11 ans (Health Canada 1996). L'utilisation de ce 99^e centile (1,138 m^3/kg-jour), au lieu d'une moyenne ou d'une médiane, pour la détermination de $NOAEL_H$ devrait se traduire par des valeurs calculées des apports tolérables quotidiens par Santé Canada 2,6 fois plus faibles, le facteur de sécurité de 3,16 utilisé pour tenir compte des différences toxicocinétiques chez l'humain (Renwick 2000; WHO 2005) ne devant pas être diminué selon la littérature actuelle (Dorne 2004; Dorne et Renwick 2005; Falk-Filipsson 2007; Dorne 2010).

Les doses internes de xénobiotiques calculées lors d'études pharmacocinétiques à base physiologique seraient 1,4 à 1,6 fois plus élevées en utilisant les moyennes des taux de ventilation alvéolaire et des débits cardiaques pour l'ensemble des activités de la journée des sujets (Article IV) au lieu de celles des individus au repos ; ce rapport de 1,4 à 1,6 fois découle, en effet, de la comparaison des ratios moyens de ventilation-perfusion variant de

1,22 à 1,53 (Article IV), avec ceux pour des sujets aux repos, soit de 0,87 chez des adultes (Zwart *et al.* 1976) et d'environ 1 chez des enfants (Motoyama 1990).

Les résultats de notre recherche confirment que le taux de ventilation minute de 20,83 L/min approximé pour une journée de travail de 8 heures et utilisé en analyse et gestion du risque pour le travailleur (Paustenbach 2001) peut être considéré comme étant conservateur. Cette valeur est supérieure 1) aux 75^{e} et 90^{e} centiles des taux de ventilation observés pour l'ensemble des activités de la journée des hommes et des femmes de poids corporel normal âgés de 25 à 96 ans respectivement (Article IV) et 2) aux centiles des taux de ventilation calculés à partir des taux quotidiens d'inhalation : les 99^{e} centiles des hommes âgées de 18 à moins de 40 ans souffrant d'embonpoint ou d'obésité (Article I) et les 97,5^{e}, 95^{e}, et 75^{e} centiles des femmes enceintes ou en lactation âgées de 23 à 55 ans de poids corporels inférieur, égal, ou supérieur aux valeurs normales respectivement (Article II). Par ailleurs, le taux quotidien d'inhalation de 0,286 m^3/kg-jour (c.-à-d. 20 m^3/jour pour un poids de 70 kg; Federal Register 1980) est inapproprié en analyse et gestion du risque pour l'ensemble de la population, ce taux étant inférieur aux 2,5^{e} centiles des taux observés chez des garçons âgés de moins d'un an, aux 10^{e} centiles des taux observés chez des garçons et des filles âgés de 2,6 mois à moins de 10 ans et 4 fois plus faible que le plus élevé des 99^{e} centiles des taux observés chez les enfants (Article III).

7 POSTFACE

L'ensemble des données énergétiques des Articles I, II et de Brochu *et al.* (2006c) sont qualifiée de « *Norme d'or* » *("Gold Standard")* par le Centre National d'Évaluation Environnementale des États-Unis pour 1) comprendre les besoins énergétiques, 2) calculer les taux quotidiens d'inhalation, ainsi que pour 3) détecter et corriger les biais des valeurs énergétiques et respiratoires de la littérature (NCEA 2007).

Les taux quotidiens d'inhalation de l'Article I et de Brochu *et al.* (2006) sont évalués par l'Institut National de Santé Publique et de l'Environnement des Pays-Bas comme étant les plus précises de la littérature (Van Engelen *et al.* 2007). Les taux de l'Article I sont publiés avec l'approche de calcul, et utilisés dans l'édition 2008 du *"Child-Specific Exposure Factors Handbook"* de l'Agence de Protection Environnementale des États-Unis, laquelle reconnaît l'Article I comme faisant partie des quatre « *Études clés sur les taux d'inhalation* » *("Keys Inhalation Rates Studies")* en évaluation et gestion du risque toxicologique pour la santé des enfants (USEPA 2008).

Les taux quotidiens d'inhalation des Articles I, II et de Brochu *et al.* (2006) sont utilisés par l'Institut National de Santé Publique du Québec dans les lignes directrices pour la réalisation des évaluations du risque toxicologique d'origine environnementale pour la santé humaine au Québec (INSPQ 2009).

Les taux quotidiens d'inhalation de l'Article I sont utilisés pour 1) mieux protéger les enfants contre l'inhalation de contaminants (De Brouwere *et al.* 2007; Van Engelen *et al.* 2007; European Commission 2008), 2) évaluer et/ou gérer les risques résultant de l'exposition de la population à l'ozone (Langstaff 2007), au bioxyde d'azote (De Brouwere *et al.* 2007), à des composés organiques (De Brouwere *et al.* 2007 ; D'Hollander *et al.* 2009 ; Buteau et Valke 2010 ; Roosens *et al.* 2010), à des métaux (European Commission. 2008; Van Holderbeke *et al.* 2008), à des insecticides (Schleier *et al.* 2008 ; Macedo *et al.* 2010), 3) valider des taux d'inhalation (Allan *et al.* 2008), 4) confirmer des faits physiologiques et/ou appuyer des démarches toxicologiques (Isukapalli *et al.* 2008; Thompson *et al.* 2008; Thompson et Grafström, 2008; Garcia *et al.* 2009a, 2009b), et 5) lors d'une étude épidémiologique sur des maladies cardiovasculaires (Pope *et al.* 2009).

CHAPITRE HUITIEME :

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DOCUMENTS COMPLÉMENTAIRES

Supplemental material for physiological daily inhalation rates for free-living individuals aged 1 month to 96 years, using data from doubly labeled water measurements: a proposal for air quality criteria, standard calculations and health risk assessment[1] (pour l'Article I).

Supplemental material for physiological daily inhalation rates for free-living pregnant and lactating adolescents and women aged 11 to 55 years, using data from doubly labeled water measurements for use in health risk assessment[1] (pour l'Article II).

Supplemental material for Derivation of physiological inhalation rates in children, adults and elderly based on nighttime and daytime respiratory parameters[2] (pour l'Article IV).

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[1]Publiés dans: *Human and Ecological Risk Assessment* et disponibles sur le site Internet du Ministère du développement durable, de l'environnement et des parcs (MDDEP), du Gouvernement du Québec aux adresses suivantes :

http://www.mddep.gouv.qc.ca/air/inhalation/index.htm (en français) ;

http://www.mddep.gouv.qc.ca/air/inhalation/index_en.htm (en anglais).

[2]A été soumis pour publication dans : *Inhalation Toxicology***,** le 13 juillet 2010.

SUPPLEMENTAL MATERIAL FOR PHYSIOLOGICAL DAILY INHALATION RATES FOR FREE-LIVING INDIVIDUALS AGED 1 MONTH TO 96 YEARS, USING DATA FROM DOUBLY LABELED WATER MEASUREMENTS: A PROPOSAL FOR AIR QUALITY CRITERIA, STANDARD CALCULATIONS AND HEALTH RISK ASSESSMENT

Pierre Brochu[1, 2, 3], Jean-François Ducré-Robitaille[1] and Jules Brodeur[2]

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[1] Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi et de l'état de l'environnement, Service des avis et expertises scientifiques, gouvernement du Québec, édifice Marie-Guyart, 7e étage, 675, boulevard René-Lévesque Est, Québec, QC, G1R 5V7, Canada.

[2] Département de santé environnementale et santé au travail, Faculté de médecine, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, QC, H3C 3J7, Canada.

[3] To whom all correspondence should be addressed.

Table Web-1 Daily energy cost for growth as a function of the total daily energy expenditure from birth to adulthood

Age group (years)	Female ECG[d] (% of TDEE[e])	Male ECG[d] (% of TDEE[e])
0 to < 0.083	43.6	46.3
0.083 to < 0.17	57.9	62.8
0.17 to < 0.25	39.3	46.5
0.25	28.2	27.3
> 0.25 to < 0.33	25.1	26.6
0.33 to < 0.42	18.3	16.9
0.42 to < 0.50	14.3	12.5
0.5 to < 0.75	6.5	6.7
0.75 to < 1	5.1	4.6
1	2.5	3.0
1.25[a]	2.3	2.7
> 1 to < 1.5[a]	2.5 to 2.0	2.7
1.5	2.0	2.1
> 1.5 to < 2[b]	2.0 to 1.7	2.0
1.75[b]	1.9	2.0
2 to < 5	1.7	1.5
5 to < 11	2.5	*n.a.*
5 to < 13	*n.a.*	3.0
11 to ≤ 18	4.2	*n.a.*
13 to ≤ 20	*n.a.*	4.2
> 18	0.0	≤ 4,2
21[c]	0.0	3.3
22[c]	0.0	2.5
23[c]	0.0	1.7
24[c]	0.0	0.8
25[c]	0.0	0.0

[a] $ECG/TDEE_{Females\ 1\text{-}1.5\ years} = Age\ (-0.01047) + 0.0357$

[b] $ECG/TDEE_{Females\ 1.5\text{-}2\ years} = Age\ (-0.00560) + 0.0284$

[c] $ECG/TDEE_{Males\ 20\text{-}25\ years} = Age\ (-0.00833) + 0.2083$

[d] ECG = stored daily energy cost for growth determined in Brochu *et al.* (2006a) based on doubly labeled water measurements (n=933) from Butte (2000), Butte *et al.* (1990, 2000) and according to Forbe (1987), Rogol *et al.* (2000), Tanner *et al.* (1975, 1996) and the IOM (2002).

[e] TDEE = total daily energy expenditure (n=2210) from Butte *et al.* (1990), Reichman *et al.* (1981, 1982) and IOM (2002).

n.a. = not applicable.

Table Web-2 Daily energy expenditure and requirement and daily energy cost for growth for newborns aged 1 month or less

Age group (days)	*n*	Body weight (kg)	Energy expenditure values and stored daily energy cost for growth (Kcal/kg-day)			
		Mean ± S.D.	BEE[e]	TDEE[f]	ECG[i]	TDER[j]
			Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
21 (3 weeks)	13[a, c]	1.2 ± 0.2	47.0 ± 3.5	62.6 ± 4.2[g]	67.8 ± 14.1	130.4 ± 16.4
32 (~ 1 month)	10[b, d]	4.7 ± 0.7	49.2 ± 4.0	64.0 ± 7.0[h]	29.0 ± 18.0	93.0 ± 16.9
33 (~ 1 month)	10[a, d]	4.8 ± 0.3	51.7 ± 4.2	67.0 ± 8.0[h]	42.0 ± 16.0	109.0 ± 15.8

[a]Formula-fed infants. [b]Breastfed infants.

[c]Healthy infants with very low birth weight (Reichman *et al.* 1981, 1982).

[d]Infants evaluated as being clinically healthy and neither underweight nor overweight (Butte *et al.* 1990).

[e]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry by Butte *et al.* (1990) and Reichman *et al.* (1981, 1982).

[f] TDEE = total daily energy expenditure.

[g]TDEEs based on nutritional balance measurements (intake and output analysis) during 3-day periods for each infant (Reichman *et al.* 1981, 1982).

[h]TDEEs based on $^{2}H_2O$ and $H_2^{18}O$ disappearance rates from urine monitored by gaz-isotope-ratio mass spectrometry during 14-day periods for each infant (Butte *et al.* 1990).

[i]ECG = stored daily energy cost for growth (Table Web-1). ECGs from Butte (2000) and Butte *et al.* (1990, 2000) were based on doubly labeled water measurements and according to Forbe (1987), Rogol *et al.* (2000), Tanner *et al.* (1975, 1996) and the IOM (2002).

jTDER = total daily energy requirement (TDEE + ECG). TDERs were converted by Brochu *et al.* (2006a) into physiological daily inhalation rates by the following equation (see Table 13): $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993).

n =number of newborns; S.D.=standard deviation.

Table Web-3 Basal and total daily energy expenditure for free-living normal-weight males and females aged 2.6 months to 96 years

Gender and age group (years)	*n*	Body weight[a] (kg) Mean ± S.D.	BEE[b] Mean ± S.D. (Kcal/day)	BEE[b] Mean ± S.D. (Kcal/kg-day)	TDEE[c] Mean ± S.D. (Kcal/day)	TDEE[c] Mean ± S.D. (Kcal/kg-day)
Males						
0.22 to < 0.5	32	6.7 ± 1.0	387.5 ± 62.0	58.1 ± 5.3	475.9 ± 126.0	71.0 ± 13.9
0.5 to < 1	40	8.8 ± 1.1	533.1 ± 62.4	60.7 ± 5.4	705.1 ± 133.0	80.1 ± 11.8
1 to < 2	35	10.6 ± 1.1	665.9 ± 70.7	62.8 ± 5.9	881.1 ± 152.1	82.7 ± 10.2
2 to < 5	25	15.3 ± 3.4	845.6 ± 153.0	56.0 ± 4.8	1,176.0 ± 273.9	77.2 ± 7.2
5 to < 7	96	19.8 ± 2.1	1,012.3 ± 90.9	51.5 ± 3.7	1,398.4 ± 191.7	71.0 ± 8.1
7 to < 11	38	28.9 ± 5.6	1,168.6 ± 141.8	41.1 ± 4.6	1,814.6 ± 340.9	63.7 ± 10.6
11 to < 23	30	58.6 ± 13.9	1,656.8 ± 244.3	29.3 ± 5.0	2,930.9 ± 621.0	51.0 ± 7.9
23 to < 30	34	70.9 ± 6.5	1,772.4 ± 152.6	25.1 ± 1.9	3,070.5 ± 492.6	43.4 ± 6.8
30 to < 40	41	71.5 ± 6.8	1,676.2 ± 151.3	23.6 ± 2.3	2,977.9 ± 441.0	41.8 ± 6.0
40 to < 65	33	71.1 ± 7.2	1,640.8 ± 250.7	23.1 ± 2.9	2,864.1 ± 471.5	40.6 ± 7.4
65 to ≤ 96	50	68.9 ± 6.7	1,480.2 ± 186.7	21.5 ± 2.1	2,285.7 ± 436.6	33.2 ± 5.5
Females						
0.22 to < 0.5	53	6.5 ± 0.9	371.2 ± 52.5	57.2 ± 5.0	460.3 ± 105.5	70.6 ± 12.3
0.5 to < 1	63	8.5 ± 1.0	506.0 ± 66.5	59.3 ± 5.0	660.9 ± 120.7	77.2 ± 10.6
1 to < 2	66	10.6 ± 1.3	630.1 ± 82.6	59.5 ± 5.1	825.9 ± 167.0	77.9 ± 13.2
2 to < 5	36	14.4 ± 3.0	775.6 ± 132.3	54.6 ± 5.3	1,083.2 ± 219.4	76.5 ± 12.4
5 to < 7	102	19.7 ± 2.3	942.9 ± 74.6	48.2 ± 4.4	1,332.2 ± 183.7	67.9 ± 8.3
7 to < 11	161	28.3 ± 4.4	1,094.8 ± 101.5	39.2 ± 4.5	1,692.8 ± 290.2	60.6 ± 10.6
11 to < 23	87	50.0 ± 8.9	1,317.0 ± 149.4	26.8 ± 3.7	2,257.7 ± 446.5	45.7 ± 8.2
23 to < 30	68	59.2 ± 6.6	1,356.7 ± 158.4	23.0 ± 2.3	2,410.7 ± 402.5	41.0 ± 7.4
30 to < 40	59	58.7 ± 5.9	1,328.5 ± 128.9	22.8 ± 2.5	2,412.2 ± 311.2	41.4 ± 6.1
40 to < 65	58	58.8 ± 5.1	1,224.8 ± 145.1	20.9 ± 2.5	2,171.0 ± 364.4	37.1 ± 6.4
65 to ≤ 96	45	57.2 ± 7.3	1,217.4 ± 152.3	21.4 ± 2.4	1,729.1 ± 382.7	30.4 ± 6.5

[a]Measured body weight. Normal-weight individuals defined according to the body mass index (BMI) cut-offs. BMIs for sub-groups are reported in Table Web-4.

[b]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry (IOM 2002).

[c]TDEE = total daily energy expenditure. TDEEs were based on $^{2}H_2O$ and $H_2{}^{18}O$ disappearance rates from urine monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods for 1252 individuals aged 2.6 months to 96 years (IOM 2002).

n =number of individuals; S.D. = standard deviation.

Table Web-4 Stored daily energy cost for growth and total daily energy requirement for free-living normal-weight males and females aged 2.6 months to 96 years

Gender and age group (years)	*n*	BMI[a] (kg/m^2) Mean ± S.D.	ECG[b] Mean ± S.D. (Kcal/day)	ECG[b] Mean ± S.D. (Kcal/kg-day)	TDER[c] Mean ± S.D. (Kcal/day)	TDER[c] Mean ± S.D. (Kcal/kg-day)
Males						
0.22 to < 0.5	32	16.8 ± 1.3	120.2 ± 41.8	18.7 ± 7.6	596.1 ± 127.2	89.7 ± 16.3
0.5 to < 1	40	17.4 ± 1.4	39.0 ± 9.5	4.5 ± 1.1	744.1 ± 138.8	84.5 ± 12.4
1 to < 2	35	16.4 ± 1.1	21.9 ± 4.2	2.1 ± 0.4	903.0 ± 154.9	84.7 ± 10.4
2 to < 5	25	15.6 ± 0.6	17.1 ± 4.0	1.1 ± 0.1	1,193.0 ± 277.8	78.3 ± 7.3
5 to < 7	96	15.3 ± 0.8	41.5 ± 5.7	2.1 ± 0.2	1,439.9 ± 197.4	73.1 ± 8.3
7 to < 11	38	16.4 ± 1.2	53.8 ± 10.1	1.9 ± 0.3	1,868.4 ± 351.0	65.6 ± 10.9
11 to < 23	30	20.2 ± 2.3	107.2 ± 32.0	1.9 ± 0.5	3,038.0 ± 646.8	52.9 ± 8.3
23 to < 30	34	22.1 ± 1.5	12.8 ± 19.9	0.2 ± 0.3	3,083.2 ± 495.8	43.6 ± 6.8
30 to < 40	41	22.5 ± 1.3	0.0 ± 0.0	0.0 ± 0.0	2,977.9 ± 441.0	41.8 ± 6.0
40 to < 65	33	22.7 ± 1.6	0.0 ± 0.0	0.0 ± 0.0	2,864.1 ± 471.5	40.6 ± 7.4
65 to ≤ 96	50	22.8 ± 1.6	0.0 ± 0.0	0.0 ± 0.0	2,285.7 ± 436.6	33.2 ± 5.5
Females						
0.22 to < 0.5	53	16.6 ± 1.1	115.1 ± 41.1	18.3 ± 7.4	575.4 ± 117.2	88.9 ± 16.4
0.5 to < 1	63	17.1 ± 1.1	38.2 ± 7.2	4.5 ± 0.8	699.0 ± 126.4	81.7 ± 11.2
1 to < 2	66	16.3 ± 1.1	17.3 ± 3.3	1.6 ± 0.4	843.2 ± 169.6	79.5 ± 13.5
2 to < 5	36	15.6 ± 0.9	18.6 ± 3.8	1.3 ± 0.2	1,101.9 ± 223.2	77.8 ± 12.6
5 to < 7	102	15.3 ± 0.9	33.6 ± 4.6	1.7 ± 0.2	1,365.9 ± 188.4	69.6 ± 8.5
7 to < 11	161	16.2 ± 1.3	42.7 ± 7.3	1.5 ± 0.3	1,735.5 ± 297.5	62.1 ± 10.9
11 to < 23	87	19.6 ± 2.1	84.2 ± 32.4	1.7 ± 0.7	2,341.9 ± 458.8	47.4 ± 8.6
23 to < 30	68	21.4 ± 1.8	0.0 ± 0.0	0.0 ± 0.0	2,410.7 ± 402.5	41.0 ± 7.4
30 to < 40	59	21.5 ± 1.6	0.0 ± 0.0	0.0 ± 0.0	2,412.2 ± 311.2	41.4 ± 6.1
40 to < 65	58	22.1 ± 1.7	0.0 ± 0.0	0.0 ± 0.0	2,171.0 ± 364.4	37.1 ± 6.4
65 to ≤ 96	45	22.0 ± 1.7	0.0 ± 0.0	0.0 ± 0.0	1,729.1 ± 382.7	30.4 ± 6.5

[a]BMI = body mass index. Normal-weight infants and toddlers aged 2 months to less than 3 years with BMIs between the 3rd and the 97th percentiles, for children and teenagers aged 4 to 19 years with BMIs corresponding to the 85th percentile or below and for adults aged 20 to 96 years with BMIs between 18.5 and 25 kg/m^2 (IOM 2002). Measured body weights for sub-groups are reported in Table Web-3.

[b]ECG = stored daily energy cost for growth. ECGs from Table Web-1 were initially added to the basic TDEEs in Table Web-3 in order to obtain the appropriate TDERs.

[c]TDER = total daily energy requirement (TDER = TDEE + ECG) .TDERs were converted by Brochu *et al.* (2006a) into physiological daily inhalation rates by the following equation (see Tables 14 and 15): $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993).

n =number of individuals; S.D. = standard deviation.

Table Web-5 Basal and total daily energy expenditure for free-living normal-weight and overweight/obese males aged 4 to 96 years

Male age group (years)	*n*	Body weight[a] (kg) Mean ± S.D.	BEE[b] Mean ± S.D. (Kcal/day)	BEE[b] Mean ± S.D. (Kcal/kg-day)	TDEE[c] Mean ± S.D. (Kcal/day)	TDEE[c] Mean ± S.D. (Kcal/kg-day)
Normal-weight						
4 to < 5.1	77	19.0 ± 1.9	991.8 ± 89.2	52.5 ± 3.8	1357.4 ± 166.5	71.8 ± 7.6
5.1 to < 9.1	52	22.6 ± 3.5	1063.2 ± 93.6	47.6 ± 4.8	1565.5 ± 247.0	69.9 ± 9.8
9.1 to <18.1	36	41.4 ± 12.1	1418.8 ± 274.3	35.3 ± 4.3	2332.0 ± 662.3	57.0 ± 8.2
18.1 to < 40.1	98	71.3 ± 6.1	1710.0 ± 165.6	24.1 ± 2.3	3040.5 ± 455.6	42.7 ± 6.2
40.1 to < 70.1	34	70.0 ± 7.8	1599.6 ± 272.8	22.9 ± 2.9	2680.9 ± 530.6	38.5 ± 7.6
70.1 to ≤ 96	38	68.9 ± 6.8	1479.7 ± 176.6	21.6 ± 2.2	2237.7 ± 411.8	32.6 ± 5.6
Overweight/obese						
4 to < 5.1	54	26.5 ± 4.9	1175.6 ± 116.5	45.1 ± 5.3	1645.6 ± 214.19	62.9 ± 7.6
5.1 to < 9.1	40	32.5 ± 9.2	1245.8 ± 176.6	39.7 ± 5.6	1863.8 ± 426.81	59.2 ± 13.3
9.1 to <18.1	33	55.8 ± 10.8	1624.2 ± 202.1	29.5 ± 2.9	2485.3 ± 338.03	45.4 ± 6.7
18.1 to < 40.1	52	98.1 ± 25.2	1970.4 ± 327.3	20.5 ± 2.3	3592.8 ± 638.93	37.5 ± 6.3
40.1 to < 70.1	81	93.2 ± 14.9	1791.9 ± 234.7	19.4 ± 1.8	3166.9 ± 654.56	34.2 ± 6.0
70.1 to ≤ 96	32	82.3 ± 10.3	1667.1 ± 265.2	20.3 ± 2.8	2509.7 ± 518.34	30.5 ± 5.3

[a]Measured body weight. Normal-weight and overweight/obese males defined according to the body mass index (BMI) cut-offs. BMIs for sub-groups are reported in Table Web-6.

[b]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry (IOM 2002).

[c]TDEE = total daily energy expenditure. TDEEs were based on $^{2}H_2O$ and $H_2^{18}O$ disappearance rates from urine monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods for 627 males aged 4 to 96 years (IOM 2002).

n =number of individuals; S.D. = standard deviation.

Table Web-6 Stored daily energy cost for growth and total daily energy requirement for free-living normal-weight and overweight/obese males aged 4 to 96 years

Male age group (years)	*n*	BMI[a] (kg/m^2) Mean ± S.D.	ECG[b] Mean ± S.D. (Kcal/day)	ECG[b] Mean ± S.D. (Kcal/kg-day)	TDER[c] Mean ± S.D. (Kcal/day)	TDER[c] Mean ± S.D. (Kcal/kg-day)
Normal-weight						
4 to < 5.1	77	15.3 ± 0.7	36.8 ± 9.1	1.9 ± 0.4	1394.2 ± 171.3	73.7 ± 7.7
5.1 to < 9.1	52	15.7 ± 1.0	46.5 ± 7.3	2.1 ± 0.3	1611.9 ± 254.4	71.9 ± 10.0
9.1 to <18.1	36	17.8 ± 1.8	82.1 ± 35.8	1.9 ± 0.4	2414.1 ± 696.7	58.9 ± 8.5
18.1 to < 40.1	98	22.3 ± 1.4	17.6 ± 37.6	0.2 ± 0.5	3058.2 ± 466.1	43.0 ± 6.4
40.1 to < 70.1	34	22.9 ± 1.7	0.0 ± 0.0	0.0 ± 0.0	2680.9 ± 530.6	38.5 ± 7.6
70.1 to ≤ 96	38	22.8 ± 1.6	0.0 ± 0.0	0.0 ± 0.0	2237.7 ± 411.8	32.6 ± 5.6
Overweight/obese						
4 to < 5.1	54	19.7 ± 2.6	46.3 ± 10.5	1.8 ± 0.4	1645.6 ± 214.2	64.7 ± 7.7
5.1 to < 9.1	40	20.1 ± 3.1	55.3 ± 12.7	1.8 ± 0.4	1863.8 ± 426.8	60.9 ± 13.7
9.1 to <18.1	33	25.7 ± 4.6	74.8 ± 13.1	1.4 ± 0.2	2485.3 ± 338.0	46.8 ± 6.9
18.1 to < 40.1	52	30.2 ± 6.8	3.5 ± 19.9	0.0 ± 0.2	3592.8 ± 638.9	37.6 ± 6.4
40.1 to < 70.1	81	30.2 ± 4.2	0.0 ± 0.0	0.0 ± 0.0	3166.9 ± 654.6	34.2 ± 6.0
70.1 to ≤ 96	32	27.8 ± 2.1	0.0 ± 0.0	0.0 ± 0.0	2509.7 ± 518.3	30.5 ± 5.3

[a]BMI = body mass index. Normal-weight children and teenagers aged 4 to 19 years with BMIs corresponding to the 85th percentile or below and normal-weight adults aged 20 to 96 years with BMIs between 18.5 and 25 kg/m^2. Overweight/obese children and teenagers aged 4 to 19 years with BMIs greater than the 85th percentile and overweight/obese adults aged 20 to 96 years with BMIs greater than 25 kg/m^2 (IOM 2002). Measured body weights for sub-groups are reported in Table Web-5.

[b]ECG = stored daily energy cost for growth. ECGs from Table Web-1 were initially added to the basic TDEEs reported in Table Web-5 in order to obtain the TDER values.

[c]TDER = total daily energy requirement (TDER = TDEE + ECG) . TDERs were converted by Brochu *et al.* (2006a) into physiological daily inhalation rates by the following equation (see Tables 16 and 18): $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993).

n =number of individuals; S.D. = standard deviation.

Table Web-7 Basal and total daily energy expenditure for free-living normal-weight and overweight/obese females aged 4 to 96 years

Female age group (years)	*n*	Body weight[a] (kg)	BEE[b]		TDEE[c]	
		Mean ± S.D.	Mean ± S.D. (Kcal/day)	Mean ± S.D. (Kcal/kg-day)	Mean ± S.D. (Kcal/day)	Mean ± S.D. (Kcal/kg-day)
Normal-weight						
4 to < 5.1	82	18.7 ± 2.0	920.8 ± 66.3	49.5 ± 4.6	1276.7 ± 155.8	68.5 ± 8.3
5.1 to < 9.1	151	25.5 ± 4.1	1051.1 ± 94.1	41.9 ± 5.2	1615.2 ± 278.7	64.0 ± 10.6
9.1 to <18.1	124	42.7 ± 11.1	1250.5 ± 157.4	30.7 ± 6.1	2048.2 ± 478.4	49.4 ± 9.9
18.1 to < 40.1	135	59.1 ± 6.3	1346.7 ± 145.9	22.9 ± 2.3	2421.0 ± 355.3	41.3 ± 6.7
40.1 to < 70.1	79	59.1 ± 5.3	1233.4 ± 151.3	21.0 ± 2.4	2103.8 ± 380.6	35.8 ± 6.7
70.1 to ≤ 96	24	54.8 ± 7.5	1182.8 ± 130.0	21.8 ± 2.6	1563.8 ± 315.8	28.8 ± 6.1
Overweight/obese						
4 to < 5.1	56	26.1 ± 5.5	1086.0 ± 133.7	42.4 ± 5.5	1499.4 ± 192.5	58.6 ± 7.6
5.1 to < 9.1	68	34.6 ± 9.9	1195.7 ± 146.5	36.1 ± 6.2	1815.5 ± 383.9	54.4 ± 11.5
9.1 to <18.1	68	59.2 ± 12.8	1474.9 ± 174.5	25.6 ± 3.9	2435.5 ± 454.1	42.2 ± 8.4
18.1 to < 40.1	76	84.4 ± 16.3	1565.7 ± 205.6	18.8 ± 2.2	2761.3 ± 372.5	33.3 ± 4.8
40.1 to < 70.1	91	81.7 ± 17.2	1422.5 ± 233.3	17.7 ± 2.1	2293.8 ± 496.7	28.5 ± 5.3
70.1 to ≤ 96	28	69.0 ± 7.8	1258.1 ± 129.1	18.4 ± 2.2	1763.2 ± 314.2	25.7 ± 4.5

[a]Measured body weight. Normal-weight and overweight/obese females defined according to the body mass index (BMI) cut-offs. BMIs for sub-groups are reported in Table Web-8.

[b]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry (IOM 2002).

[c]TDEE = total daily energy expenditure. TDEEs were based on $^{2}H_2O$ and $H_2{}^{18}O$ disappearance rates from urine monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods for 982 females aged 4 to 96 years (IOM 2002).

n =number of individuals; S.D. = standard deviation.

Table Web-8 Stored daily energy cost for growth and total daily energy requirement for free-living normal-weight and overweight/obese females aged 4 to 96 years

Female age group (years)	*n*	BMI[a] (kg/m^2) Mean ± S.D.	ECG[b] Mean ± S.D. (Kcal/day)	ECG[b] Mean ± S.D. (Kcal/kg-day)	TDER[c] Mean ± S.D. (Kcal/day)	TDER[c] Mean ± S.D. (Kcal/kg-day)
Normal-weight						
4 to < 5.1	82	15.3 ± 0.8	30.4 ± 5.7	1.6 ± 0.3	1307.1 ± 160.0	70.1 ± 8.4
5.1 to < 9.1	151	15.9 ± 1.2	40.8 ± 7.0	1.6 ± 0.3	1656.0 ± 285.7	65.7 ± 10.9
9.1 to <18.1	124	18.4 ± 2.2	75.0 ± 28.5	1.7 ± 0.4	2123.2 ± 503.8	51.1 ± 10.0
18.1 to < 40.1	135	21.5 ± 1.7	0.0 ± 0.0	0.0 ± 0.0	2421.0 ± 355.3	41.3 ± 6.7
40.1 to < 70.1	79	22.2 ± 1.7	0.0 ± 0.0	0.0 ± 0.0	2103.8 ± 380.6	35.8 ± 6.7
70.1 to ≤ 96	24	21.8 ± 1.6	0.0 ± 0.0	0.0 ± 0.0	1563.8 ± 315.8	28.8 ± 6.1
Overweight/obese						
4 to < 5.1	56	19.5 ± 2.8	35.6 ± 7.9	1.4 ± 0.2	1535.0 ± 199.3	59.9 ± 7.8
5.1 to < 9.1	68	21.0 ± 4.0	45.8 ± 9.7	1.4 ± 0.3	1861.3 ± 393.6	55.8 ± 11.8
9.1 to <18.1	68	25.2 ± 3.7	81.2 ± 29.2	1.4 ± 0.4	2516.7 ± 476.2	43.5 ± 8.6
18.1 to < 40.1	76	30.7 ± 5.5	0.0 ± 0.0	0.0 ± 0.0	2761.3 ± 372.5	33.3 ± 4.8
40.1 to < 70.1	91	30.7 ± 5.7	0.0 ± 0.0	0.0 ± 0.0	2293.8 ± 496.7	28.5 ± 5.3
70.1 to ≤ 96	28	27.6 ± 2.1	0.0 ± 0.0	0.0 ± 0.0	1763.2 ± 314.2	25.7 ± 4.5

[a]BMI = body mass index. Normal-weight children and teenagers aged 4 to 19 years with BMIs corresponding to the 85th percentile or below and normal-weight adults aged 20 to 96 years with BMIs between 18.5 and 25 kg/m^2. Overweight/obese children and teenagers aged 4 to 19 years with BMIs greater than the 85th percentile and overweight/obese adults aged 20 to 96 years with BMIs greater than 25 kg/m^2 (IOM 2002). Measured body weights for sub-groups are reported in Table Web-7.

[b]ECG = stored daily energy cost for growth. ECGs from Table Web-1 were initially added to the basic TDEEs reported in Table Web-7 in order to obtain the TDER values.

[c]TDER = total daily energy requirement (TDER = TDEE + ECG) . TDERs were converted by Brochu *et al.* (2006a) into physiological daily inhalation rates by the following equation (see Tables 17 and 19): $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and $V_E/VO_2 = 27$ (Layton 1993).

n =number of individuals; S.D. = standard deviation.

Table Web-9 Mann-Whitney statistical results for the calculation of differences between mean ages of normal-weight and overweight/obese male and female sub-groups

Age group (years)	Age group span[a] (years)	Mann-Whitney statistical results					
		Male sub-groups[b]			Female sub-groups[c]		
		p value[d]	*Difference*[e]	D/S[f] (%)	*p* value[d]	*Difference*[e]	D/S[f] (%)
4 to < 5.1	1	0.7071	*n.s.d.*	0%	<0.0001	~ 7.6 days	~ 2%
5.1 to < 9.1	4	0.0437	~ 3 months	~6%	<0.0001	~ 4.2 months	~ 9%
9.1 to <18.1	9	0.0126	~ 1.5 years	~17%	0.0280	~ 1 year	~11%
18.1 to < 40.1	22	0.0002	~ 4 years	~18%	0.0489	~ 1.5 years	~7%
40.1 to < 70.1	30	0.9780	*n.s.d.*	0%	0.2380	*n.s.d.*	0%
70.1 to ≤ 96	26	0.3203	*n.s.d.*	0%	0.5257	*n.s.d.*	0%

[a]Age span based on minimum and maximum limits of age groups for the selection of subjects from the IOM database (2002) for each sample (or sub-group).

[b]Mann-Whitney tests performed between normal-weight and overweight/obese male sub-groups reported in Tables Web-5 and Web-6 and Tables 16 and 18 in Brochu *et al.* (2006a).

[c]Mann-Whitney tests performed between normal-weight and overweight/obese female sub-groups reported in Tables Web-7 and Web-8 and Tables 17 and 19 in Brochu *et al.* (2006a).

[d]Mean ages between normal-weight and overweight/obese age groups are statistically different when p< 0.05.

[e]Difference between mean ages of normal-weight and overweight/obese sub-groups.

[f]D = Difference between mean ages of sub-groups; S = age group span.

n.s.s. = no statistically significative difference between mean ages of sub-groups.

Table Web-10 Basal and total daily energy expenditure, stored daily energy cost for growth and total daily energy requirement for free-living adults from less affluent societies

Subjects[a]	*n*	Age (years)			BMI[g] (kg/m^2)	Body weight (kg)	Daily energy expenditure and requirement and stored daily energy cost for growth (kcal/kg-day)			
		Mean ± S.D.	Percentile[f] 1st	99th	Mean ± S.D.	Mean ± S.D.	BEE[h]	TDEE[i]	ECG[j]	TDER[k]
Males										
Sub-group A[b]	6	26.8 ± 4.4	16.6	37.0	19.6 ± 0.6	55.0 ± 4.0	27.6	49.4	0.5	49.9
Sub-group B[b]	5	25.8 ± 4.1	16.3	35.3	20.6 ± 1.0	58.4 ± 2.6	26.9	46.6	0.4	47.0
Sub-group C[c]	16	35.0 ± 1.0	32.7	37.3	21.0 ± 2.2	61.6 ± 6.4	24.5	72.9	0.0	72.9
Females										
Sub-group D[d]	15	35.7 ± 6.8	19.9	51.5	24.2 ± 5.1	54.1 ± 12.4	23.7	38.2	0.0	38.2
Sub-group E[e]	10	30.0 ± 2.6	24.0	36.0	19.8 ± 2.1	49.4 ± 5.3	24.5	48.6	0.0	48.6
Sub-group F[e]	7	26.0 ± 3.4	18.1	33.9	20.0 ± 2.3	50.2 ± 6.0	26.5	45.9	0.0	45.9

[a]Mean ages, BMIs, body weights, BEEs and TDEEs are reported in Black *et al.* (1996).

[b]Thin Chilean laborers. [c]Gambian laborers. [d]Guatemalan mothers. [e]Gambian farmers.

[f]1st and 99th percentiles based on standard deviations associated to mean ages of sub-groups assuming normality.

[g]BMI = body mass index.

[h]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry (Black *et al*. 1996).

[i]TDEE = total daily energy expenditure. TDEEs were based on ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods.

[j]ECG = stored daily energy cost for growth.The TDEEs of normal-weight subjects from the IOM (2002) selected according to the 1st and 99th age percentiles for adult sub-groups from less affluent societies were used to determine their ECGs considering guidelines from Table Web-1. ECGs of 0.5 kcal/kg-day (n=79) for sub-group A and 0.4 kcal/kg-day (n=74) for sub-group B were calculated.

[k]TDER = total daily energy requirement (TDEE + ECG). TDERs were converted in Brochu *et al.* (2006a) into physiological daily inhalation rates by the following equation (see Table 20): $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and VE/VO_2 = 27 (Layton 1993).

n =number of individuals; S.D. = standard deviation.

Table Web-11 Basal and total daily energy expenditure, stored daily energy cost for growth and total daily energy requirement for free-living females with anorexia nervosa and for control sub-groups

Female sub-groups[a]	*n*	Age (years) Mean ± S.D.	Age Percentile[b] 1st	Age Percentile[b] 99th	BMI[c] (kg/m^2) Mean ± S.D.	Body weight (kg) Mean ± S.D.	Daily energy expenditure and requirement and stored daily energy cost for growth (kcal/kg-day) BEE[d]	TDEE[e]	ECG[f]	TDER[g]
Females with anorexia nervosa										
Sub-group A	8	27.8 ± 5.2	15.7	39.9	15.2 ± 5.6	43.0 ± 5.6	26.1	67.3	0.1	67.4
Sub-group B	6	24.5 ± 6.9	*n.a.*	*n.a.*	15.7 ± 2.8	42.5 ± 9.4	23.5	46.3	0.0	46.3
Sub-group C	3	36.0 ± 10.8	*n.a.*	*n.a.*	15.0 ± 0.9	40.6 ± 1.0	27.8	43.1	0.0	43.1
Control sub-groups										
Sub-group A	11	24.5 ± 4.2	14.7	34.3	20.0 ± 1.3	57.5 ± 5.1	23	40.9	1.0	41.9
Sub-group B	6	24.8 ± 7.0	*n.a.*	*n.a.*	21.6 ± 2.3	42.5 ± 9.4	31	46.5	0.0	46.5

[a]Mean ages, BMIs, body weights, BEEs and TDEEs are reported in Black *et al.* (1996).
[b]1st and 99th percentiles based on standard deviations associated to mean ages of sub-groups assuming normality.
[c]BMI = body mass index.
[d]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry.
[e]TDEE = total daily energy expenditure. TDEEs were based on $^{2}H_2O$ and $H_2{}^{18}O$ disappearance rates from urine monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods.
[f]ECG = stored daily energy cost for growth. TDEEs of normal-weight females from IOM (2002) selected according to the 1st and 99th age percentiles for sub-groups A were used to determine their ECGs considering guidelines from Table Web-1. ECGs of 0.1 kcal/kg-day (n=147) for sub-group A with anorexia nervosa and 1.0 kcal/kg-day (n=142) for the control sub-group A were calculated. Standard age deviations of other sub-groups were too large for normality assumption and thus for ECG calculation.
[g]TDER = total daily energy requirement (TDEE + ECG). TDERs were converted in Brochu *et al.* (2006a) into physiological daily inhalation rates by the following equation (see Table 21): $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993).
n =number of individuals; S.D. = standard deviation.
n.a. = not applicable.

Table Web-12 Basal and total daily energy expenditure, stored daily energy cost for growth and total daily energy requirement for free-living athletes, explorers and soldiers during extreme physical activity

Subjects[a]	*n*	Age (years)			BMI[f] (kg/m^2)	Body weight (kg)	Daily energy expenditure and requirement and stored daily energy cost for growth (kcal/kg-day)			
		Mean ± S.D.	Percentile[e] 1st	Percentile[e] 99th	Mean ± S.D.	Mean ± S.D.	BEE[g]	TDEE[h]	ECG[i]	TDER[j]
Male athletes										
Swimmers	5	19.8 ± 1.6	16.1	23.5	21.8 ± 1.8	80.3 ± 7.2	23.6	49.5	1.5	50.9
Cyclists[b]	4	24 ± n.d.	n.a.	n.a.	n.d. ± n.d.	68.4 ± n.d.	25.1	117.6	1.0	118.5
Cross-country skiers	4	26 ± 1.8	21.8	30.2	23.1 ± 0.1	75.1 ± 4.9	27.8	96.2	0.6	96.8
Mountaineers[c]	3	35.3 ± 4.0	26.0	44.6	20.9 ± 0.8	64.3 ± 8.6	22.4	54.4	0.0	54.4
Female athletes									0.0	
Swimmers	3	20.7 ± 1.5	17.2	24.2	22.3 ± 2.5	67.8 ± 2.0	22.0	38.4	0.3	38.7
During rigorous training	4	25 ± n.d.	n.a.	n.a.	n.d. ± n.d.	50.6 ± 3.2	24.7	68.9	0.0	68.9
In calorimeter	9	26 ± 3.3	18.3	33.7	19.1 ± 0.8	52.4 ± 4.1	26.5	32.0	0.0	32.0
Runners during training	9	26 ± 3.3	18.3	33.7	19.4 ± 0.7	51.6 ± 3.5	27.0	54.7	0.0	54.7
Cross-country skiers	4	25 ± 2.2	19.9	30.1	19.8 ± 1.5	54.4 ± 5.1	28.7	80.4	0.0	80.4
Mountaineers[c]	2	37.5 ± 6.4	22.6	52.4	19.9 ± 2.2	54.0 ± 1.4	26.5	53.0	0.0	53.0
Endurance runners	9	n.d. ± n.d.	n.a.	n.a.	19.3 ± 1.7	55.3 ± 6.2	23.6	53.0	n.a.	53.0
Male explorers [d]	2	38.15 ± 2.0	n.a.	n.a.	n.d. ± n.d.	78.5 ± 9.2	22.5	100.6	0.0	100.6
Male soldiers										
Jungle training	4	22.5 ± 3.3	14.8	30.2	22.5 ± 1.7	73.8 ± 8.9	24.4	64.3	0.9	65.1
Field training	14	27.1 ± 5.4	14.5	39.7	24 ± 1.3	75.2 ± 5.7	24.0	45.8	0.4	46.2
Winter training	23	27.1 ± 3.8	18.3	35.9	25.2 ± 1.7	79.8 ± 6.3	22.8	61.5	0.5	62.0
High mountain training	23	27.1 ± 3.8	18.3	35.9	25.2 ± 1.7	79.8 ± 6.3	22.8	89.2	0.7	89.9
Base camp training	23	27.1 ± 3.8	18.3	35.9	25.2 ± 1.7	79.8 ± 6.3	22.8	45.4	0.3	45.8
Active service	15	20 ± n.d.	n.a.	n.a.	22.8 ± 1.9	70.7 ± 5.3	24.7	60.1	2.5	62.6
Arctic training	10	n.d. ± n.d.	n.a.	n.a.	25.7 ± n.d.	77.0 ± 7.5	22.8	55.2	n.a.	55.2

[a]Mean ages, BMIs, body weights, BEE and TDEEs are reported in Black *et al.* (1996).

[b]Over the 21 days of the Tour de France. [c]On Mount Everest. [d]In the first 20 days of sled hauling across the Arctic by adults aged 35.3 and 41 years.

[e]1st and 99th percentiles based on standard deviations associated to mean ages of subjects. [f]BMI = body mass index.

[g]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry.

[h]TDEE = total daily energy expenditure. TDEEs were based on $^{2}H_2O$ and $H_2{}^{18}O$ disappearance rates from urine monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods.

[i]ECG = stored daily energy cost for growth. ECGs for normal weight individuals in the IOM (2002) corresponding to the 1th and 99th age percentiles for athlete, explorer and soldier sub-groups based on guidelines from Table Web-1. ECGs of 1.5 kcal/kg-day (n=19), 1.0 kcal/kg-day (n=3), 0.6 kcal/kg-day (n=41) for male athletes and 0.3 kcal/kg-day (n=30) for female athletes were calculated. ECGs of 0.9 kcal/kg-day (n=53), 0.4 kcal/kg-day (n=93), 0.5, 0.7, 0.3 kcal/kg-day (n=72) and 2.5 kcal/kg-day (n=3) for male soldiers were also calculated.

[j]TDER = total daily energy requirement (TDEE + ECG). TDERs were converted in Brochu *et al.* (2006a) into physiological daily inhalation rates by the following equation (see Table 22): $TDER*H*(V_E/VO_2)*10^{-3}$. H = 0.21 L of O_2/Kcal and V_E/VO_2 = 27 (Layton 1993). *n* =number of individuals; S.D. = standard deviation.

SUPPLEMENTAL MATERIAL FOR PHYSIOLOGICAL DAILY INHALATION RATES FOR FREE-LIVING PREGNANT AND LACTATING ADOLESCENTS AND WOMEN AGED 11 TO 55 YEARS, USING DATA FROM DOUBLY LABELED WATER MEASUREMENTS FOR USE IN HEALTH RISK ASSESSMENT

Pierre Brochu[1, 2, 3], Jean-François Ducré-Robitaille[1] and Jules Brodeur[2]

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[1] Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi et de l'état de l'environnement, Service des avis et expertises scientifiques, gouvernement du Québec, édifice Marie-Guyart, 7e étage, 675, boulevard René-Lévesque Est, Québec, QC, G1R 5V7, Canada.

[2] Département de santé environnementale et santé au travail, Faculté de médecine, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, QC, H3C 3J7, Canada.

[3] To whom all correspondence should be addressed.

Table Web-1 Anthropometrical and energy expenditure measurements for free-living non-pregnant and non-lactating adolescents and women aged 11 to 55 years

Weight status[a] and age group (years)	*n*	BMI[a] (kg/m^2) Mean ± S.D.	Body weight (kg) Mean ± S.D.	Mean energy expenditure values for non-pregnant and non-lactating females, Mean ± S.D.: BEE[b] (Kcal/day)	BEE[b] (Kcal/kg-day)	TDEE[c] (Kcal/kg-day)	ECG[d] (Kcal/kg-day)	TDER[e] (Kcal/day)	TDER[e] (Kcal/kg-day)	DMET[f] Mean ± S.D. *(unitless)*
Underweight										
11 to < 23	50	18.1 ± 1.2	44.45 ± 6.4	1263.7 ± 135.7	28.8 ± 3.3	46.9 ± 7.8	1.9 ± 0.4	2148.5 ± 366.5	48.8 ± 8.1	1.70 ± 0.24
23 to < 30	17	19.1 ± 0.4	53.18 ± 5.2	1292.5 ± 137.9	24.4 ± 2.6	46.5 ± 8.4	0.0 ± 0.0	2456.2 ± 399.5	46.5 ± 8.4	1.91 ± 0.31
30 to 55	14	19.3 ± 0.4	51.91 ± 3.1	1262.8 ± 108.2	24.4 ± 2.0	43.9 ± 4.8	0.0 ± 0.0	2273.3 ± 247.6	43.9 ± 4.8	1.81 ± 0.26
Normal-weight										
11 to < 23	57	22.3 ± 1.6	58.2 ± 5.9	1407.5 ± 136.1	24.3 ± 2.5	42.9 ± 8.6	1.5 ± 0.7	2566.5 ± 475.9	44.4 ± 9.0	1.83 ± 0.35
23 to < 30	54	22.4 ± 1.6	61.5 ± 5.8	1374.0 ± 155.4	22.3 ± 2.1	38.9 ± 6.1	0.0 ± 0.0	2396.7 ± 393.2	38.9 ± 6.1	1.75 ± 0.27
30 to 55	61	22.3 ± 1.5	60.7 ± 5.7	1336.5 ± 140.3	22.1 ± 2.5	40.4 ± 6.2	0.0 ± 0.0	2438.2 ± 337.7	40.4 ± 6.2	1.84 ± 0.26
Overweight/obese										
11 to < 23	15	30.6 ± 4.6	81.3 ± 15.4	1623.1 ± 154.9	20.3 ± 2.8	35.1 ± 5.5	1.3 ± 0.6	2930.3 ± 513.9	36.4 ± 5.9	1.81 ± 0.31
23 to < 30	25	30.4 ± 4.7	84.2 ± 15.6	1554.2 ± 219.4	18.7 ± 2.0	32.7 ± 4.4	0.0 ± 0.0	2724.6 ± 409.9	32.7 ± 4.4	1.77 ± 0.25
30 to 55	64	32.1 ± 6.3	88.2 ± 18.6	1588.7 ± 232.6	18.3 ± 2.3	32.4 ± 5.5	0.0 ± 0.0	2798.1 ± 444.6	32.4 ± 5.5	1.77 ± 0.22

[a]Underweight, normal-weight and overweight/obese pregnant females are defined as those having BMIs lower than 19.8 kg/m^2, varying between 19.8 and 26 kg/m^2, and higher than 26 kg/m^2 respectively, for desirable gestational weight gain and deposition of maternal fat and, associated with the best outcome for both infants, in terms of birth weight, and mothers, in terms of delivery complications and postpartum weight retention (IOM, 1990). BMI = body mass index.

[b]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry (IOM 2002).

[c]TDEE = total daily energy expenditure, based on doubly labeled water measurements: $^{2}H_2O$ and $H_2{}^{18}O$ disappearance rates from urine were monitored in each subject by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods (Butte 2000; Butte *et al.* 2000; IOM 2002).

[d]ECG = stored daily energy cost for growth (Brochu *et al.* 2006a).

[e]TDER = total daily energy requirement (ECG + TDEE).

[f]Daily metabolic equivalent or daily BEE multiplier, also known as physical activity levels or PAL when adding the ECG.

n= number of individuals; S.D. = standard deviation.

Table Web-2 Anthropometrical and energy expenditure measurements for free-living normal-weight males aged 11 to 55 years for comparison purposes with female values

Weight status[a] and age group (years)	*n*	BMI[a] (kg/m^2) Mean ± S.D.	Body weight (kg) Mean ± S.D.	Mean energy expenditure values for males Mean ± S.D.: BEE[b] (Kcal/day)	BEE[b] (Kcal/kg-day)	TDEE[c] (Kcal/kg-day)	ECG[d] (Kcal/kg-day)	TDER[e] (Kcal/day)	TDER[e] (Kcal/kg-day)	DMET[f] Mean ± S.D. *(unitless)*
Normal-weight										
11 to < 23	21	21.8 ± 1.7	68.0 ± 7.8	1767.8 ± 179.8	26.3 ± 3.9	47.5 ± 7.2	1.7 ± 0.5	3325.4 ± 502.1	49.2 ± 7.6	1.88 ± 0.21
23 to < 30	36	22.5 ± 1.6	71.9 ± 6.3	1771.3 ± 147.5	24.7 ± 2.1	42.6 ± 6.2	0.2 ± 0.3	3073.8 ± 482.0	42.8 ± 6.3	1.73 ± 0.22
30 to 55	74	23.1 ± 1.7	73.0 ± 6.6	1690.4 ± 194.4	23.2 ± 2.5	41.3 ± 6.2	0.0 ± 0.0	2999.8 ± 446.2	41.3 ± 6.2	1.78 ± 0.22

[a]Normal-weight males are defined in Table Web-1 according to body mass index cutoffs for females varying between 19.8 and 26 kg/m^2 associated with the best outcome for both infants, in terms of birth weight, and mothers, in terms of delivery complications and postpartum weight retention (IOM, 1990).

[b]BEE = basal energy expenditure (BMR expressed on a 24-hour basis) measured by indirect calorimetry (IOM 2002).

[c]TDEE = total daily energy expenditure, based on doubly labeled water measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from urine were monitored in each subject by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods (IOM 2002).

[d]ECG = stored daily energy cost for growth (Brochu *et al.* 2006a).

[e]TDER = total daily energy requirement (ECG + TDEE).

[f]Daily metabolic equivalent or daily BEE multiplier, also known as physical activity levels or PAL when adding the ECG.

n= number of individuals; S.D. = standard deviation.

Table Web-3 Daily energy cost and gestational weight gain measured for free-living women during pregnancy

Pregnant female weight status[a]	*n*	BMI[a] (kg/m²)	Mean daily energy cost[b] (± S.D.) (kcal/day)			Gestational duration[b] (weeks)
			9th week	22nd week	36th week	Mean ± S.D.
Underweight	17	< 19.8	137 ± 368	163 ± 512	294 ± 602	38.3 ± 1.6
Normal-weight	34	19.8 to 26.0	32 ± 461	356 ± 416	496 ± 368	39.3 ± 1.1
Overweight/obese	12	> 26.1	367 ± 585	441 ± 755	434 ± 806	39.6 ± 1.2
Pregnant female weight status[a]	***n***	**BMI[a] (kg/m²)**	**Mean gestational weight gain[c] (± S.D.) (g/day)**			**Complete gestational weight gain[c] (kg)**
			0 to 9th week	**9th to 22nd week**	**22nd to 36th week**	**Mean ± S.D.**
Underweight	17	< 19.8	33.0 ± 42.1	66.8 ± 18.7	53.7 ± 20.6	15.0 ± 3.8
Normal-weight	34	19.8 to 26.0	6.8 ± 46.6	52.7 ± 19.6	81.5 ± 21.3	14.5 ± 4.5
Overweight/obese	12	> 26.1	68.1 ± 69.1	71.0 ± 31.5	83.2 ± 37.7	17.9 ± 5.4

[a]Underweight, normal-weight and overweight/obese pregnant females are defined as those having BMIs lower than 19.8 kg/m^2, varying between 19.8 and 26 kg/m^2, and higher than 26 kg/m^2 respectively, for desirable gestational weight gain and deposition of maternal fat and, associated with the best outcome for both infants, in terms of birth weight, and for mothers, in terms of delivery complications and postpartum weight retention (IOM, 1990). BMI = body mass index.

[b]Data measured by Butte *et al.* (2004). Mean daily energy costs for pregnancy are based on the doubly labeled water method, room respiration calorimeters and body composition measurements: ^2H_2O and $H_2{}^{18}O$ disappearance rates from saliva samples were monitored by gaz-isotope-ratio mass spectrometry during 13 day periods in 63 females.

[c]Weight gain measured by Butte *et al.* (2004). Bodyweights measured with an electronic balance before pregnancy; at the 9th, 22nd, and 36th week of pregnancy and recorded weekly by each women throughout the gestation duration up to conception.

n= number of individuals; S.D. = standard deviation.

Table Web-4 Daily energy cost and postpartum weight loss for free-living mothers during lactation

Lactating female weight status[a]	*n*	BMI[a] (kg/m^2)	Mean daily energy cost (± S.D.) (Kcal/day)		Mean postpartum weight loss[d] (± S.D.)			
			Milk synthesis[b]	Energy output[c]	Birth weight (kg)	0 to 2nd week[e] (kg)	2nd to 6th week[f] (g/day)	6th to 27th week[f] (g/day)
Underweight	17	< 19.8	107.9 ± 21.3	539.3 ± 106.3	3.38 ± 0.44	-10.1 ± 12.5	-11.9 ± 41.3	-17.3 ± 13.8
Normal-weight	34	19.8 to 26.0	107.9 ± 21.3	539.3 ± 106.3	3.55 ± 0.39	-9.0 ± 18.8	-23.4 ± 55.9	-15.5 ± 20.0
Overweight/obese	12	> 26.1	107.9 ± 21.3	539.3 ± 106.3	3.82 ± 0.47	-10.6 ± 26.0	-26.6 ± 53.2	-14.4 ± 25.3

[a]Underweight, normal-weight and overweight/obese female status as defined in Table 2 according to BMI cutoffs associated with the best outcome for both infants, in terms of birth weight, and mothers, in terms of delivery complications and postpartum weight retention (IOM, 1990). BMI = body mass index.

[b]Mean milk synthesis corresponding to 20% of milk-energy output (Goldberg *et al.* 1991; n=10).

[c]Mean milk-energy output based on DLW measurements reported in IOM (2002) for lactating females aged 26 to 40 years (n=28) with BMIs varying between 18.5 to 23.7 kg/m^2.

^2H_2O and $H_2{}^{18}O$ disappearance rates from urine were monitored by gaz-isotope-ratio mass spectrometry during 7 to 21-day periods (IOM 2002).

[d]Birth weights and mother weight losses reported in Butte *et al.* (2004). The bodyweight of each woman was measured with an electronic balance at the 2nd, 6th, and 27th postpartum week.

[e]Including placenta, amniotic fluid, maternal fat and newborn weights. Standard deviations are not corrected for the weight correlation at 0 and 2 weeks.

[f]Including maternal fat weight.

n= number of individuals; S.D. = standard deviation.

Table Web-5 Distribution of bodyweight percentiles for underweight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	Number of subjects[b] <u>n</u> $_{Exp.}$ or n $_{Sim.}$	Bodyweights[c] (kg) Mean ± S.D.	Percentiles 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females	<u>50</u>	44.5 ± 6.4	31.9	33.9	36.2	40.1	44.5	48.8	52.7	55.0	57.0	59.4
	Prepregnancy 0 week	5000	44.9 ± 6.1	35.1	35.5	36.6	40.2	45.6	48.9	52.7	55.7	57.1	57.8
	Pregnancy 9th week	5000	47.0 ± 6.7	35.3	36.5	38.1	41.8	47.1	51.5	55.7	58.2	59.7	61.1
	Pregnancy 22nd week	5000	53.1 ± 6.9	41.2	42.3	44.2	48.0	53.1	57.8	62.0	64.4	66.2	67.9
	Pregnancy 36th week	5000	58.3 ± 7.2	45.8	47.2	49.1	53.1	58.1	63.1	67.5	70.1	72.1	73.7
	Postpartum 6th week	5000	56.1 ± 7.4	36.2	37.9	40.3	44.2	49.3	54.5	58.9	61.2	63.3	65.1
	Postpartum 27th week	5000	53.6 ± 7.7	32.8	34.5	37.1	41.4	46.6	52.0	56.4	59.1	61.4	63.6
23 to < 30	Non-pregnant females	<u>17</u>	53.2 ± 5.2	43.0	44.7	46.5	49.7	53.2	56.7	59.8	61.7	63.3	65.2
	Prepregnancy 0 week	5000	53.1 ± 5.0	43.2	44.8	47.4	50.9	52.0	56.3	61.1	61.9	62.1	62.1
	Pregnancy 9th week	5000	55.2 ± 5.6	44.9	46.5	48.6	51.6	54.8	59.0	63.0	64.7	66.0	67.1
	Pregnancy 22nd week	5000	61.3 ± 5.9	50.1	51.9	54.0	57.4	61.0	65.2	69.2	71.0	72.4	73.6
	Pregnancy 36th week	5000	66.5 ± 6.3	55.1	56.8	58.8	62.4	66.2	70.4	74.8	77.1	78.4	79.7
	Postpartum 6th week	5000	64.3 ± 6.5	45.5	47.5	49.4	53.1	57.2	61.6	66.1	68.4	70.0	71.5
	Postpartum 27th week	5000	61.8 ± 6.8	42.5	44.4	46.5	50.2	54.7	59.2	63.8	66.1	67.9	69.5
30 to 55	Non-pregnant females	<u>14</u>	51.9 ± 3.1	46.9	46.9	48.0	49.8	51.9	54.0	55.8	56.9	57.9	59.0
	Prepregnancy 0 week	5000	51.9 ± 2.9	47.0	47.4	48.5	49.5	51.5	53.7	56.3	57.2	57.5	57.5
	Pregnancy 9th week	5000	54.0 ± 3.9	46.9	47.9	49.2	51.3	53.7	56.6	59.1	60.4	61.6	62.7
	Pregnancy 22nd week	5000	60.1 ± 4.3	52.2	53.4	54.7	57.2	59.9	62.8	65.4	67.0	68.3	69.5
	Pregnancy 36th week	5000	65.4 ± 4.7	56.7	58.2	59.7	62.3	65.3	68.6	71.4	73.1	74.6	75.8
	Postpartum 6th week	5000	63.2 ± 5.1	47.0	48.6	50.1	53.0	56.4	59.8	63.0	65.0	66.6	67.9
	Postpartum 27th week	5000	60.6 ± 5.5	43.6	45.1	47.0	50.2	53.8	57.4	60.6	62.4	64.0	65.9

[a]Underweight females are defined as those having a body mass index lower than 19.8 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] <u>n</u>$_{Exp.}$ = number of experimental non-pregnant and non-lactating females; n$_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Underweight non-pregnant and non-lactating female bodyweights (IOM 2002; n=81) were integrated with day-to-day variations of bodyweight (gain and loss) for underweight females (Butte *et al.* 2004; n=17) by using Monte Carlo simulations and based on a normal distribution. Means and standard deviations of input weight measurements are reported in Tables Web-1, Web-3 and Web-4.

Table Web-6 Distribution of bodyweight percentiles for normal-weight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	Number of subjects[b] $n_{Exp.}$ or $n_{Sim.}$	Bodyweights[c] (kg) Mean ± S.D.	Percentiles 2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
11 to < 23	Non-pregnant females	57	58.2 ± 5.9	46.6	48.5	50.6	54.2	58.2	62.2	65.8	68.0	69.9	72.0
	Prepregnancy 0 week	5000	58.2 ± 5.9	46.4	47.5	50.7	54.7	58.1	62.2	65.0	66.5	69.4	70.9
	Pregnancy 9th week	5000	58.6 ± 6.6	46.0	47.8	50.4	54.5	58.8	63.0	66.6	68.8	70.6	72.4
	Pregnancy 22nd week	5000	63.4 ± 6.9	50.4	52.3	54.7	59.0	63.5	67.9	71.9	74.1	75.8	77.6
	Pregnancy 36th week	5000	71.4 ± 7.2	57.7	59.7	62.5	66.7	71.4	76.1	80.5	83.0	85.0	87.1
	Postpartum 6th week	5000	68.6 ± 7.5	48.7	50.7	53.2	57.8	62.6	67.5	71.6	74.1	76.3	78.7
	Postpartum 27th week	5000	66.4 ± 8.1	45.7	47.9	50.4	55.3	60.5	65.7	70.5	73.4	75.7	77.9
23 to < 30	Non-pregnant females	54	61.5 ± 5.8	50.2	52.0	54.1	57.6	61.5	65.4	68.8	70.9	72.7	74.9
	Prepregnancy 0 week	5000	61.6 ± 5.7	51.4	52.5	54.2	57.3	61.4	65.7	68.4	70.2	72.2	74.2
	Pregnancy 9th week	5000	62.0 ± 6.4	50.2	51.6	53.7	57.5	61.9	66.6	70.1	72.2	74.2	75.9
	Pregnancy 22nd week	5000	66.8 ± 6.7	54.9	56.5	58.4	62.2	66.8	71.4	75.5	77.7	79.6	81.5
	Pregnancy 36th week	5000	74.8 ± 7.0	62.1	63.8	65.9	69.8	74.6	79.6	84.0	86.3	88.2	90.2
	Postpartum 6th week	5000	72.1 ± 7.3	52.7	54.7	57.1	61.2	66.2	71.2	75.7	78.2	80.0	82.0
	Postpartum 27th week	5000	69.8 ± 7.9	49.6	51.7	54.1	58.7	64.0	68.9	73.9	76.6	78.6	80.9
30 to 55	Non-pregnant females	61	60.7 ± 5.7	51.3	51.3	53.4	56.8	60.7	64.6	68.1	70.2	72.0	74.1
	Prepregnancy 0 week	5000	60.7 ± 5.7	51.8	52.5	53.0	56.2	61.2	64.0	68.8	70.5	71.7	72.5
	Pregnancy 9th week	5000	61.1 ± 6.4	49.9	51.1	52.8	56.5	61.3	65.3	69.0	71.4	73.3	74.8
	Pregnancy 22nd week	5000	65.9 ± 6.7	54.0	55.5	57.3	61.3	66.1	70.4	74.7	76.9	78.9	80.5
	Pregnancy 36th week	5000	73.9 ± 7.0	61.3	62.7	64.7	69.0	74.1	78.6	82.8	85.2	86.9	88.7
	Postpartum 6th week	5000	71.3 ± 7.3	52.1	53.7	55.8	60.3	65.5	70.3	74.7	77.1	79.0	80.8
	Postpartum 27th week	5000	68.9 ± 7.9	48.5	50.4	52.9	57.8	63.3	68.5	73.1	75.7	77.7	79.8

[a]Normal-weight females are defined as those having a body mass index varying between 19.8 and 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Normal-weight non-pregnant and non-lactating female bodyweights (IOM 2002; n=172) were integrated with day-to-day variations of bodyweight (gain and loss) for normal-weight females (Butte *et al.* 2004; n=34) by using Monte Carlo simulations and based on a normal distribution. Means and standard deviations of input weight measurements are reported in Tables Web-1, Web-3 and Web-4.

Table Web-7 Distribution of bodyweight percentiles for overweight/obese[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	*Number of subjects*[b] *n Exp.* or *n Sim.*	Bodyweights[c] (kg) Mean ± S.D.	Percentiles 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females	15	81.3 ± 15.4	51.2	56.0	61.6	71.0	81.3	91.7	101.1	106.7	111.5	117.2
	Prepregnancy 0 week	5000	81.3 ± 14.8	64.4	65.5	68.9	73.2	78.3	84.4	92.0	113.4	128.0	130.4
	Pregnancy 9th week	5000	85.6 ± 15.3	66.8	68.8	71.5	76.8	82.8	89.8	99.5	119.9	131.3	136.1
	Pregnancy 22nd week	5000	92.0 ± 15.6	72.3	74.7	77.8	83.1	89.4	96.5	105.7	126.8	138.9	142.7
	Pregnancy 36th week	5000	97.1 ± 17.5	71.7	74.9	78.9	86.3	94.7	104.1	116.2	133.1	145.4	153.1
	Postpartum 6th week	5000	94.5 ± 17.8	61.0	64.6	69.2	77.0	85.7	94.6	106.2	121.5	134.3	142.0
	Postpartum 27th week	5000	92.4 ± 18.1	57.7	62.0	66.7	74.8	84.0	93.6	106.8	121.9	133.0	140.8
23 to < 30	Non-pregnant females	25	84.2 ± 15.6	53.7	58.6	64.3	73.7	84.2	94.7	104.2	109.8	114.7	120.4
	Prepregnancy 0 week	5000	84.0 ± 14.7	66.0	67.3	68.8	75.8	81.6	87.0	100.5	116.6	127.6	134.6
	Pregnancy 9th week	5000	88.4 ± 15.2	67.7	69.7	72.7	79.0	86.1	93.4	104.8	116.3	129.6	139.1
	Pregnancy 22nd week	5000	94.8 ± 15.4	73.4	75.7	79.0	85.3	92.4	100.4	112.3	124.9	137.4	144.9
	Pregnancy 36th week	5000	100.3 ± 17.8	73.2	76.6	80.6	88.4	97.8	108.3	120.9	132.6	144.1	154.4
	Postpartum 6th week	5000	97.7 ± 18.1	63.2	66.6	71.2	79.1	89.0	99.6	112.4	123.7	135.4	144.4
	Postpartum 27th week	5000	95.5 ± 18.6	60.2	63.5	68.2	76.6	86.4	97.9	111.5	122.7	135.1	145.2
30 to 55	Non-pregnant females	64	88.2 ± 18.6	57.7	57.7	64.4	75.7	88.2	100.8	112.0	118.8	124.6	131.5
	Prepregnancy 0 week	5000	87.8 ± 18.0	64.8	68.0	72.4	75.5	83.2	95.5	110.0	123.8	136.3	148.0
	Pregnancy 9th week	5000	92.1 ± 18.6	67.7	71.0	74.3	80.1	87.7	100.1	114.1	127.1	141.5	153.5
	Pregnancy 22nd week	5000	98.6 ± 18.7	73.1	76.3	80.2	86.4	94.6	106.5	121.2	133.9	147.4	159.9
	Pregnancy 36th week	5000	103.8 ± 20.5	73.2	77.1	81.9	90.3	100.7	113.2	127.8	140.9	153.4	163.4
	Postpartum 6th week	5000	101.2 ± 20.7	63.2	67.2	72.0	80.5	91.3	103.9	118.1	130.8	143.2	154.8
	Postpartum 27th week	5000	99.0 ± 21.1	60.8	64.9	70.0	78.4	89.5	102.2	117.7	131.5	144.7	155.5

[a]Overweight/obese females are defined as those having a body mass index higher than 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]Overweight/obese non-pregnant and non-lactating female bodyweights (IOM 2002; n=104) were integrated with day-to-day variations of bodyweight (gain and loss) for overweight/obese females (Butte *et al.* 2004; n=12) by using Monte Carlo simulations and based on a normal distribution. Means and standard deviations of input weight measurements are reported in Tables Web-1, Web-3 and Web-4.

Table Web-8 Distribution of total daily energy requirement (kcal/day) percentiles for free-living underweight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks.

Age group (years)	Progression of the reproductive cycle	*Number of subjects*[b] *n*E xp. or *n* Sim.	Total daily energy requirements[c] (kcal/day) Mean ± S.D.	Percentiles 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females	50	2148 ± 366	1430	1546	1679	1901	2148	2396	2618	2751	2867	3001
	Prepregnancy 0 week	5000	2165 ± 343	1585	1650	1718	1903	2148	2420	2580	2730	2862	2981
	Pregnancy 9th week	5000	2307 ± 585	1644	1708	1799	1993	2243	2530	2767	2993	3246	3546
	Pregnancy 22nd week	5000	2327 ± 617	1643	1707	1806	2002	2259	2553	2859	3093	3449	3972
	Pregnancy 36th week	5000	2457 ± 622	1699	1768	1875	2099	2352	2662	3026	3367	3867	4532
	Postpartum	5000	2814 ± 371	2186	2251	2350	2549	2804	3066	3283	3426	3561	3674
23 to < 30	Non-pregnant females	17	2456 ± 400	1673	1799	1944	2187	2456	2456	2968	3113	3239	3386
	Prepregnancy 0 week	5000	2453 ± 382	2007	2013	2027	2131	2454	2702	2824	3141	3447	3522
	Pregnancy 9th week	5000	2592 ± 648	2033	2049	2092	2210	2556	2795	3075	3487	3770	4427
	Pregnancy 22nd week	5000	2608 ± 548	2032	2046	2091	2209	2562	2804	3168	3554	3832	4230
	Pregnancy 36th week	5000	2751 ± 706	2070	2101	2154	2310	2669	2935	3476	3808	4252	5033
	Postpartum	5000	3098 ± 402	2535	2581	2643	2779	3068	3333	3540	3820	4087	4219
30 to 55	Non-pregnant females	14	2273 ± 248	1788	1866	1956	2106	2273	2273	2591	2681	2759	2849
	Prepregnancy 0 week	5000	2276 ± 239	1890	1914	1990	2114	2203	2466	2644	2669	2677	2678
	Pregnancy 9th week	5000	2417 ± 511	1931	1984	2062	2173	2336	2617	2768	2936	3164	3543
	Pregnancy 22nd week	5000	2438 ± 528	1932	1980	2061	2174	2339	2618	2784	3002	3368	3985
	Pregnancy 36th week	5000	2578 ± 613	1989	2045	2124	2241	2464	2729	3031	3365	3789	4507
	Postpartum	5000	2925 ± 271	2468	2525	2603	2731	2888	3117	3310	3385	3442	3490

[a]Underweight females are defined as those having a body mass index lower than 19.8 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]TDERs of underweight non-pregnant and non-lactating females (IOM, 2002; n=81) including the energy cost for growth (Brochu *et al.* 2006a; n=93) have been integrated with day-to-day variations of energy costs for pregnancy in underweight females (Butte *et al.* 2004, n=17) as well as milk-energy synthesis (Goldberg *et al.* 1991, n= 10) and breast-energy output (IOM 2002, n=28) by using Monte Carlo simulations. TDER differences throughout pregnancy and lactation were simulated with lognormal and normal distributions respectively (5000 TDERs/sub-group). Input energetic physiological measurements are based on disappearance rates of deuterium (^2H) and heavy oxygen-18 (^{18}O) monitored by gas-isotope-ratio mass spectrometry in urine or saliva samples of free-living females for a 7 to 21-day period per subject (Tables Web-1, Web-3 and Web-4).

Table Web-9 Distribution of total daily energy requirement (kcal/day) percentiles for free-living normal-weight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	**Progression of the reproductive cycle**	***Number of subjects*** [b] ***n**$_{E xp.}$ **or n**$_{Sim.}$*	**Total daily energy requirements[c] (kcal/day)** Mean ± S.D.	Percentiles 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
	Non-pregnant females	<u>57</u>	2567 ± 476	1634	1784	1957	2245	2567	2888	3176	3349	3499	3674
	Prepregnancy 0 week	5000	2,566 ± 475	1566	1713	1910	2345	2607	2803	3059	3300	3531	3688
11 to < 23	Pregnancy 9th week	5000	2,586 ± 503	1583	1724	1920	2370	2621	2829	3088	3350	3597	3721
	Pregnancy 22nd week	5000	2,924 ± 626	1822	1986	2212	2596	2881	3195	3655	3979	4315	4643
	Pregnancy 36th week	5000	3,061 ± 609	1938	2106	2336	2721	3038	3361	3785	4087	4363	4690
	Postpartum	5000	3,213 ± 496	2187	2334	2534	2953	3252	3484	3750	4000	4237	4389
	Non-pregnant females	<u>54</u>	2397 ± 393	1626	1750	1893	2131	2397	2662	2901	3043	3167	3311
	Prepregnancy 0 week	5000	2,408 ± 404	1711	1797	1877	2137	2421	2628	2908	3152	3276	3367
23 to < 30	Pregnancy 9th week	5000	2,458 ± 1291	1727	1801	1883	2142	2428	2652	2951	3169	3295	3499
	Pregnancy 22nd week	5000	2,764 ± 564	1909	2010	2161	2410	2704	3051	3440	3678	3956	4397
	Pregnancy 36th week	5000	2,912 ± 543	2030	2132	2281	2545	2853	3229	3630	3850	4068	4311
	Postpartum	5000	3,058 ± 421	2303	2397	2520	2775	3051	3307	3617	3800	3931	4032
	Non-pregnant females	<u>61</u>	2438 ± 338	1776	1883	2005	2210	2438	2666	2871	2994	3100	3224
	Prepregnancy 0 week	5000	2,433 ± 323	1908	1952	2025	2212	2401	2629	2892	3002	3095	3230
30 to 55	Pregnancy 9th week	5000	2,461 ± 493	1915	1964	2036	2218	2411	2648	2905	3025	3165	3545
	Pregnancy 22nd week	5000	2,787 ± 526	2095	2162	2272	2460	2699	3035	3369	3661	3964	4327
	Pregnancy 36th week	5000	2,921 ± 485	2219	2296	2393	2590	2858	3178	3523	3753	4017	4308
	Postpartum	5000	3,080 ± 345	2512	2583	2671	2841	3049	3291	3547	3686	3804	3918

[a]Normal-weight females are defined as those having a body mass index varying between 19.8 and 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] <u>n</u>$_{Exp.}$ = number of experimental non-pregnant and non-lactating females; n$_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]TDERs of normal-weight non-pregnant and non-lactating females (IOM, 2002; n=172) including the energy cost for growth (Brochu *et al.* 2006a; n=93) have been integrated with day-to-day variations of energy costs for pregnancy in normal-weight females (Butte *et al.* 2004, n=34) as well as milk-energy synthesis (Goldberg *et al.* 1991, n= 10) and breast-energy output (IOM 2002, n=28) by using Monte Carlo simulations. TDER differences throughout pregnancy and lactation were simulated with lognormal and normal distributions respectively (5000 TDERs/sub-group). Input energetic physiological measurements are based on disappearance rates of deuterium (^{2}H) and heavy oxygen-18 (^{18}O) monitored by gas-isotope-ratio mass spectrometry in urine or saliva samples of free-living females for a 7 to 21-day period per subject (Tables Web-1, Web-3 and Web-4).

Table Web-10 Distribution of total daily energy requirement (kcal/day) percentiles for free-living overweight/obese[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	*Number of subjects*[b] $n_{Exp.}$ or $n_{Sim.}$	Total daily energy requirements[c] (kcal/day) Mean ± S.D.	Percentiles 2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
11 to < 23	Non-pregnant females	15	2930 ± 514	1923	2085	2272	2584	2930	3277	3589	3776	3938	4126
	Prepregnancy 0 week	5000	2935 ± 495	1708	1801	2139	2738	3037	3266	3470	3538	3552	3556
	Pregnancy 9[th] week	5000	3301 ± 839	1928	2084	2471	2982	3284	3604	3962	4312	4758	5384
	Pregnancy 22[nd] week	5000	3378 ± 900	1938	2120	2496	2992	3319	3645	4083	4520	5056	5944
	Pregnancy 36[th] week	5000	3383 ± 1064	1888	2062	2470	2989	3318	3662	4096	4597	5270	6151
	Postpartum	5000	3580 ± 511	2350	2477	2777	3384	3673	3917	4122	4214	4269	4316
23 to < 30	Non-pregnant females	25	2725 ± 410	1921	2050	2199	2448	2725	3001	3250	3399	3528	3678
	Prepregnancy 0 week	5000	2728 ± 401	1838	2105	2314	2532	2733	2974	3168	3432	3568	3600
	Pregnancy 9[th] week	5000	3097 ± 769	2034	2296	2476	2727	3004	3315	3765	4111	4576	5272
	Pregnancy 22[nd] week	5000	3162 ± 808	2075	2336	2517	2759	3043	3422	3872	4334	4895	5766
	Pregnancy 36[th] week	5000	3177 ± 897	2054	2316	2499	2750	3033	3423	3952	4497	5175	6223
	Postpartum	5000	3377 ± 420	2429	2665	2908	3147	3374	3610	3855	4062	4194	4290
30 to 55	Non-pregnant females	64	2798 ± 445	1927	2067	2228	2498	2798	3098	3368	3529	3669	3832
	Prepregnancy 0 week	5000	2792 ± 433	1993	2103	2256	2522	2786	3031	3312	3434	3589	3886
	Pregnancy 9[th] week	5000	3166 ± 735	2196	2313	2480	2766	3076	3413	3853	4281	4706	5369
	Pregnancy 22[nd] week	5000	3238 ± 860	2210	2346	2512	2774	3095	3485	4009	4530	5059	6066
	Pregnancy 36[th] week	5000	3218 ± 821	2198	2324	2477	2752	3078	3468	3988	4507	5088	5931
	Postpartum	5000	3439 ± 453	2609	2736	2888	3150	3438	3701	3962	4107	4267	4546

[a]Overweight/obese females are defined as those having a body mass index higher than 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]TDERs of overweight/obese non-pregnant and non-lactating females (IOM, 2002; n=104) including the energy cost for growth (Brochu *et al.* 2006a; n=93) have been integrated with day-to-day variations of energy costs for pregnancy in overweight/obese females (Butte *et al.* 2004, n=12) as well as milk-energy synthesis (Goldberg *et al.* 1991, n= 10) and breast-energy output (IOM 2002, n=28) by using Monte Carlo simulations. TDER differences throughout pregnancy and lactation were simulated with lognormal and normal distributions respectively (5000 TDERs/sub-group). Input energetic physiological measurements are based on disappearance rates of deuterium (^{2}H) and heavy oxygen-18 (^{18}O) monitored by gas-isotope-ratio mass spectrometry in urine or saliva samples of free-living females for a 7 to 21-day period per subject (Tables Web-1, Web-3 and Web-4).

Table Web-11 Distribution of total daily energy requirement (kcal/kg-day) percentiles for free-living underweight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	Number of subjects[b] $n_{Exp.}$ or $n_{Sim.}$	Total daily energy requirements[c] (kcal/kg-day) Mean ± S.D.	Percentiles 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
11 to < 23	Non-pregnant females	50	48.8 ± 8.1	32.9	35.5	38.4	43.3	48.8	48.8	59.2	62.1	64.6	67.6
	Prepregnancy 0 week	5000	48.8 ± 7.9	36.1	36.8	38.4	42.0	48.8	55.2	59.5	60.8	62.8	65.0
	Pregnancy 9th week	5000	49.8 ± 14.2	34.8	35.9	37.6	42.2	48.7	55.3	61.4	65.3	70.5	80.4
	Pregnancy 22nd week	5000	44.3 ± 12.0	30.9	31.9	33.5	37.7	43.3	48.9	54.2	58.9	65.3	77.9
	Pregnancy 36th week	5000	42.5 ± 10.9	29.2	30.3	32.0	36.0	41.3	47.0	53.1	59.5	66.5	75.6
	Postpartum 6th week	5000	50.8 ± 7.9	42.6	44.3	46.6	51.1	57.2	64.5	71.3	75.7	78.8	82.3
	Postpartum 27th week	5000	53.4 ± 8.9	44.0	45.9	48.4	53.4	60.3	68.4	76.5	81.4	85.6	90.0
23 to < 30	Non-pregnant females	17	46.5 ± 8.4	30.1	32.8	35.8	40.9	46.5	46.5	57.3	60.3	62.9	66.0
	Prepregnancy 0 week	5000	46.5 ± 8.1	36.1	36.3	37.3	40.3	45.3	50.2	60.3	63.7	63.8	63.8
	Pregnancy 9th week	5000	47.4 ± 12.6	34.9	35.8	37.2	40.2	45.4	51.8	60.5	64.8	68.7	76.5
	Pregnancy 22nd week	5000	42.9 ± 9.8	31.5	32.4	33.7	36.5	41.1	46.9	54.5	58.5	62.5	68.8
	Pregnancy 36th week	5000	41.7 ± 11.4	29.9	30.7	31.9	35.0	39.5	45.6	52.9	57.8	64.2	76.6
	Postpartum 6th week	5000	48.6 ± 7.8	41.0	42.3	44.2	48.0	53.1	59.5	67.1	71.5	75.5	79.1
	Postpartum 27th week	5000	50.7 ± 8.5	42.5	44.0	46.0	49.7	55.3	62.5	70.7	75.9	80.7	84.4
30 to 55	Non-pregnant females	14	43.9 ± 4.8	34.5	36.0	37.8	40.7	43.9	43.9	50.0	51.7	53.2	54.9
	Prepregnancy 0 week	5000	43.9 ± 4.6	35.8	36.6	38.8	40.9	42.7	47.3	50.4	51.9	52.6	52.7
	Pregnancy 9th week	5000	44.9 ± 9.7	34.9	36.2	37.7	40.2	43.7	47.9	52.4	55.8	60.3	68.5
	Pregnancy 22nd week	5000	40.7 ± 9.2	31.6	32.6	33.9	36.2	39.5	43.3	47.6	51.9	58.0	68.4
	Pregnancy 36th week	5000	39.6 ± 9.7	29.7	30.7	32.0	34.2	37.8	42.2	47.4	53.1	60.6	69.6
	Postpartum 6th week	5000	46.5 ± 5.3	41.6	43.1	45.0	48.0	51.9	56.3	60.6	63.0	65.1	67.6
	Postpartum 27th week	5000	48.6 ± 5.9	43.0	44.6	46.4	49.7	54.1	59.2	64.4	67.2	69.7	72.2

[a]Underweight females are defined as those having a body mass index lower than 19.8 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]TDERs and bodyweights of underweight non-pregnant and non-lactating females (IOM, 2002; n=81) were integrated with day-to-day weight changes (gain and loss) and variations of energy cost for underweight pregnant females (Butte *et al.* 2004, n=17) and breastfeeding mothers (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by using Monte Carlo simulations. TDER differences throughout pregnancy and postpartum weeks were simulated with lognormal and normal distributions respectively, while weight variations are based on normal distribution (5000 TDERs/sub-group). Means and standard deviations of input weight and energetic physiological measurements are reported in Tables Web-1, Web-3 and Web-4.

Table Web-12 Distribution of total daily energy requirement (kcal/kg-day) percentiles for free-living normal-weight[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	Number of subjects[b] $\underline{n}_{Exp.}$ or $n_{Sim.}$	Total daily energy requirements[c] (kcal/kg-day) Mean ± S.D.	Percentiles 2.5[nd]	5[th]	10[th]	25[th]	50[th]	75[th]	90[th]	95[th]	97.5[th]	99[th]
11 to < 23	Non-pregnant females	<u>57</u>	44.4 ± 9.0	26.8	29.6	32.9	38.3	44.4	50.5	55.9	59.2	62.0	65.3
	Prepregnancy 0 week	5000	44.4 ± 8.9	28.0	29.8	33.4	38.5	43.4	49.8	57.1	59.7	62.4	63.7
	Pregnancy 9th week	5000	44.5 ± 9.6	28.3	30.0	33.5	38.5	43.5	50.2	57.0	60.5	63.3	67.0
	Pregnancy 22nd week	5000	46.6 ± 11.0	29.4	31.5	34.7	39.3	45.2	52.5	59.7	64.7	69.4	76.9
	Pregnancy 36th week	5000	43.2 ± 9.4	27.5	29.7	32.4	36.9	42.5	48.9	55.5	59.6	63.5	68.0
	Postpartum 6th week	5000	47.3 ± 8.6	35.5	37.6	40.3	45.1	50.9	57.6	64.7	68.8	71.9	75.0
	Postpartum 27th week	5000	49.0 ± 9.3	36.8	38.9	41.5	46.5	52.9	60.2	68.2	73.4	77.3	80.7
23 to < 30	Non-pregnant females	<u>54</u>	38.9 ± 6.1	27.0	28.9	31.1	34.8	38.9	43.0	46.7	49.0	50.9	53.1
	Prepregnancy 0 week	5000	39.2 ± 6.2	29.5	30.6	31.9	35.0	38.4	42.7	47.4	50.3	53.2	55.9
	Pregnancy 9th week	5000	39.9 ± 24.4	29.0	30.1	31.5	34.8	38.5	43.1	47.9	51.1	54.3	59.2
	Pregnancy 22nd week	5000	41.6 ± 8.7	29.7	31.0	32.6	35.9	40.2	45.4	51.7	56.0	60.4	67.4
	Pregnancy 36th week	5000	39.1 ± 7.4	27.8	29.0	30.7	33.9	38.0	43.1	48.6	52.5	55.4	58.9
	Postpartum 6th week	5000	42.7 ± 6.2	35.2	36.5	38.4	41.7	46.0	50.9	55.5	58.6	61.4	64.0
	Postpartum 27th week	5000	44.2 ± 6.8	36.0	37.5	39.4	43.0	47.7	52.9	57.9	61.4	64.6	68.3
30 to 55	Non-pregnant females	<u>61</u>	40.4 ± 6.2	28.3	30.2	32.5	36.2	40.4	44.6	48.4	50.6	52.6	54.9
	Prepregnancy 0 week	5000	40.4 ± 6.1	29.8	30.7	32.9	35.7	40.4	44.5	48.5	50.6	52.3	53.3
	Pregnancy 9th week	5000	40.7 ± 8.9	29.4	30.6	32.6	35.7	40.0	44.8	49.4	51.7	53.7	57.3
	Pregnancy 22nd week	5000	42.7 ± 8.9	29.9	31.3	33.3	36.9	41.5	47.3	52.9	56.8	61.8	67.5
	Pregnancy 36th week	5000	39.8 ± 7.5	28.4	29.6	31.3	34.7	39.1	44.2	49.1	52.8	56.4	60.6
	Postpartum 6th week	5000	43.6 ± 6.4	35.5	36.8	38.7	42.4	47.3	52.7	57.4	59.9	61.9	64.4
	Postpartum 27th week	5000	45.2 ± 7.0	36.3	37.9	39.7	43.7	49.0	54.9	60.1	63.1	65.6	68.4

[a]Normal-weight females are defined as those having a body mass index varying between 19.8 and 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $\underline{n}_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]TDERs and bodyweights of normal-weight non-pregnant and non-lactating females (IOM, 2002; n=172) were integrated with day-to-day weight changes (gain and loss) and variations of energy cost for normal-weight pregnant females (Butte *et al.* 2004, n=34) and breastfeeding mothers (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by using Monte Carlo simulations. TDER differences throughout pregnancy and postpartum weeks were simulated with lognormal and normal distributions respectively, while weight variations are based on normal distribution (5000 TDERs/sub-group). Means and standard deviations of input weight and energetic physiological measurements are reported in Tables Web-1, Web-3 and Web-4.

Table Web-13 Distribution of total daily energy requirement (kcal/kg-day) percentiles for free-living overweight/obese[a] adolescents and women aged 11 to 55 years during pregnancy and postpartum weeks

Age group (years)	Progression of the reproductive cycle	*Number of subjects*[b] *n*	Total daily energy requirements[c] (kcal/kg-day) Mean ± S.D.	Percentiles 2.5nd	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
	Non-pregnant females	15	36.4 ± 5.9	24.8	26.7	28.8	32.4	36.4	40.4	43.9	46.1	47.9	50.1
	Prepregnancy 0 week	5000	36.4 ± 5.7	25.4	25.7	27.0	33.1	37.8	40.0	42.4	44.6	45.5	45.6
	Pregnancy 9th week	5000	39.1 ± 9.8	25.4	26.5	28.8	34.1	38.5	42.6	47.7	51.9	57.1	66.6
11 to < 23	Pregnancy 22nd week	5000	37.1 ± 10.2	23.7	24.7	26.6	31.9	36.2	40.7	46.2	50.6	56.4	66.2
	Pregnancy 36th week	5000	35.5 ± 11.9	22.2	23.5	25.4	29.6	34.1	38.9	44.4	49.5	56.5	68.5
	Postpartum 6th week	5000	38.7 ± 7.0	27.9	29.4	31.7	36.7	41.5	46.5	51.4	54.6	57.8	61.3
	Postpartum 27th week	5000	39.7 ± 7.4	28.4	29.8	32.5	37.4	42.8	48.0	53.1	57.0	60.4	64.6
	Non-pregnant females	25	32.7 ± 4.4	24.0	25.4	27.0	29.7	32.7	35.7	38.4	40.0	41.4	43.0
	Prepregnancy 0 week	5000	32.8 ± 4.4	24.4	25.2	27.4	30.3	32.3	35.4	39.1	41.1	41.5	41.7
	Pregnancy 9th week	5000	35.5 ± 8.8	25.2	26.3	28.0	30.7	34.1	38.6	43.6	48.4	54.5	61.6
23 to < 30	Pregnancy 22nd week	5000	33.8 ± 8.9	23.8	24.9	26.5	29.0	32.1	36.6	41.8	46.6	52.1	60.2
	Pregnancy 36th week	5000	32.3 ± 9.8	21.9	23.0	24.3	26.9	30.4	35.2	41.3	47.3	54.6	65.5
	Postpartum 6th week	5000	35.3 ± 5.9	27.2	28.3	30.0	33.3	37.5	42.0	46.7	49.7	52.6	56.1
	Postpartum 27th week	5000	36.2 ± 6.4	27.8	29.1	30.9	34.2	38.5	43.3	48.6	51.9	55.4	59.3
	Non-pregnant females	64	32.4 ± 5.5	21.6	23.3	25.3	28.7	32.4	36.1	39.5	41.5	43.3	45.3
	Prepregnancy 0 week	5000	32.5 ± 5.5	20.8	22.5	24.9	29.2	32.6	36.2	39.0	39.9	41.5	43.3
	Pregnancy 9th week	5000	35.2 ± 8.9	22.2	23.8	26.3	30.3	34.1	38.7	44.4	49.0	53.8	60.2
30 to 55	Pregnancy 22nd week	5000	33.5 ± 9.1	21.2	22.8	25.2	28.7	32.2	36.6	41.7	47.0	53.7	63.4
	Pregnancy 36th week	5000	31.8 ± 8.9	19.7	21.3	23.3	26.5	30.3	34.8	41.2	46.2	51.7	59.9
	Postpartum 6th week	5000	35.0 ± 6.6	24.4	25.9	28.3	32.6	37.3	42.1	46.9	50.3	53.1	55.7
	Postpartum 27th week	5000	35.8 ± 7.1	25.0	26.5	29.0	33.2	38.0	43.2	48.4	52.1	55.6	59.8

[a]Overweight/obese females are defined as those having a body mass index higher than 26 kg/m^2 in prepregnancy (weight classification explained in Table Web-1).

[b] $n_{Exp.}$ = number of experimental non-pregnant and non-lactating females; $n_{Sim.}$ = number of simulated females. S.D. = standard deviation.

[c]TDERs and bodyweights of overweight/obese non-pregnant and non-lactating females (IOM, 2002; n=104) were integrated with day-to-day weight changes (gain and loss) and variations of energy cost for overweight/obese pregnant females (Butte *et al.* 2004, n=12) and breastfeeding mothers (Goldberg *et al.* 1991, n= 10; IOM 2002, n=28) by using Monte Carlo simulations. TDER differences throughout pregnancy and postpartum weeks were simulated with lognormal and normal distributions respectively, while weight variations are based on normal distribution (5000 TDERs/sub-group). Means and standard deviations of input weight and energetic physiological measurements are reported in Tables Web-1, Web-3 and Web-4.

SUPPLEMENTAL MATERIAL FOR DERIVATION OF PHYSIOLOGICAL INHALATION RATES IN CHILDREN, ADULTS AND ELDERLY BASED ON NIGHTTIME AND DAYTIME RESPIRATORY PARAMETERS

Pierre Brochu[1, 2, 3], Jules Brodeur[2] and Kannan Krishnan[2]

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[1] Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi et de l'état de l'environnement, Service des avis et expertises scientifiques, gouvernement du Québec, édifice Marie-Guyart, 7e étage, 675, boulevard René-Lévesque Est, Québec, QC, G1R 5V7, Canada.

[2] Département de santé environnementale et santé au travail, Faculté de médecine, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, QC, H3C 3J7, Canada.

[6] To whom all correspondence should be addressed.

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