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Développement de seuils toxicologiques et prédiction de doses internes pour l'exposition professionnelle aux substances organiques à partir de leurs structures moléculaires

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Résumé

Plusieurs substances chimiques ne possèdent pas de valeurs limites d'exposition professionnelle (VLEP) pour protéger la santé des travailleurs. L'objectif de la recherche effectuée dans le cadre de cette thèse était de développer des outils et modèles pharmacocinétiques, en se basant sur la structure moléculaire, pour permettre la caractérisation des risques sanitaires associés aux substances organiques sans VLEP. Trois sous-objectifs furent identifiés : i) développer des seuils de préoccupation toxicologique basés sur la dose absorbée (DA) pour usage en milieu professionnel (OTTC); ii) développer un cadre structuré de modélisation intégrée relation quantitative propriété-propriété (QPPR)-pharmacocinétique à base physiologique (PBPK) chez l'humain pour prédiction à haut débit de la pharmacocinétique, dont la dose interne d'exposition (DI), de substances organiques inhalées; et finalement iii) développer des OTTC et des modèles prédictifs de valeurs limites provisoires pour l'exposition professionnelle, tous basés sur la DI. Premièrement, un jeu de données composé de 280 substances organiques fut constitué avec des données de VLEP et de propriétés physico-chimiques et toxicologiques (p. ex., coefficients de partage (P), classes de Cramer [toxicités faible (classe I), modérée (classe II) et élevée (classe III)]). Deuxièmement, la considération de la biodisponibilité (de par le $P_{sang:air}$) a permis de prédire la DA de chaque substance par le travailleur et des analyses de distributions de ces DA d'identifier des OTTC. Troisièmement, pour prédire les DI (en mode 'batch'), un cadre de modélisation intégrée QPPR-PBPK chez l'humain fut paramétré à l'aide des algorithmes (c.à.d. QPPR) pour les coefficients de partage et la clairance hépatique, entre autres. Trois mesures de DI furent estimées : (i) l'aire sous la courbe des concentrations veineuses en fonction du temps, jusqu'à 24 h (AUC_{24}), (ii) le taux journalier de quantité de produit-mère métabolisé ($RMET_{24}$) et (iii) la concentration veineuse maximale après 8 h d'exposition. La fiabilité des prédictions fut évaluée par des analyses croisées de l'incertitude et de la sensibilité. Quatrièmement, des analyses des distributions des DI furent effectuées suivies de celles de régression linéaire simple entre DI et VLEP. Tandis que les OTTC prédits en utilisant la DA étaient de 0,15; 0,0085; et 0,006 mmol/jour au 10^e centile pour les classes I-III, ils étaient de 1,5; 0,09 et 0,03 mmol/jour au 25^e centile. Les analyses de performance ont indiqué que la fiabilité des AUC_{24}, prédites avec le cadre de modélisation

proposé, était de modérée à élevée pour 55% des substances, 46% de celles-ci ayant des AUC_{24} de fiabilité élevée. Des corrélations élevées et significatives ont été observées entre les mesures de DI et la VLEP, particulièrement la $RMET_{24}$ ($r^2 = 0.81$; n = 276). Utilisant $RMET_{24}$, les OTTC basés sur la DI proposés étaient de $5{,}61\times10^{-2}$ et 9×10^{-4} mmol/jour au 10^{e} centile pour les classes I et III respectivement, alors qu'ils étaient de $4{,}55\times10^{-1}$ et $8{,}50\times10^{-3}$ mmol/jour au 25^{e} centile. Ainsi, pour la première fois, cette recherche a permis de développer des seuils toxicologiques basés sur la structure moléculaire des substances, afin de permettre des évaluations préliminaires du risque sanitaire et la priorisation des substances sans VLEP en milieu de travail.

Mots-clés : valeur limite d'exposition professionnelle, seuil de préoccupation toxicologique, modélisation pharmacocinétique à base physiologique, relation quantitative propriété-propriété, analyse du risque sanitaire en milieu de travail.

Abstract

Occupational Exposure Limits (OELs) are valuable tools for workers' health risk characterization and protection. However, in workplace, many substances do not have OELs. The main objective of this research project was to develop tools and predictive pharmacokinetic models, using molecular structure information, for occupational risk assessment and characterization of data-poor organic chemicals. Thus, three specific objectives were pursued as follows: i) derive occupational thresholds of toxicological concern (OTTCs) based on absorbed dose; ii) develop a quantitative property-property relationship (QPPR)-based human physiologically based pharmacokinetic (PBPK) modeling framework for high-throughput predictions of inhalation toxicokinetics, including the internal dose (ID), of organic chemicals; and finally, iii) derive ID-based OTTCs as well as quantitative models for predicting screening-level limit values for occupational exposure in data-poor situations. First, a dataset of 280 organic chemicals consisting of data on OEL as well as physicochemical and toxicologic parameters (i.e., partition coefficients (P), Cramer class of toxicity [low (class I), intermediate (class II) and high (class III)]) was compiled. Second, the dose absorbed in workers was predicted for each chemical in the dataset from consideration of the bioavailability (*as per* the QPPR-derived $P_{blood:air}$). Subsequently, distributional analyses of these absorbed doses were performed to identify the OTTCs. Third, for ID estimations (in 'batch' mode), a QPPR-based human PBPK modeling framework was parameterized with QPPR-derived values of $P_{blood:air}$, $P_{tissu:air}$, and hepatic clearance. Three ID metrics were identified for investigation: (i) the daily area under the venous blood concentration *versus* time curve (AUC_{24}), (ii) the daily rate of the amount of parent chemical metabolized ($RMET_{24}$) and (iii) the maximum venous blood concentration after an 8-h work shift. Using AUC_{24}, the resulting model's reliability was evaluated based on joint sensitivity and uncertainty analyses. Fourth, distributional analyses of the predicted ID were further performed to derive ID-based OTTCs; and simple linear regression analyses performed to study and quantify the relationship between the ID metrics and OEL. Based on the absorbed dose, the derived OTTCs were 0.15, 0.0085, and 0.006 mmol/day at the 10^{th} percentile level for Cramer classes I-III respectively, while these values were 1.5, 0.09 and 0.03 mmol/day at the 25^{th} percentile level. The reliability analysis indicated that the AUC_{24} values predicted with the proposed PBPK modeling framework were moderate to highly reliable

for 55% of the chemicals, with 46% exhibiting highly reliable values. High and significant correlations were observed between the OEL and the ID metrics predicted with the modeling framework, specifically $RMET_{24}$ ($r^2 = 0.81$; n = 276). Based on $RMET_{24}$, the proposed ID-based OTTCs were 5.61×10^{-2} and 9×10^{-4} mmol/day at the 10^{th} percentile level for classes I and III, respectively, while they were 4.55×10^{-1} and 8.50×10^{-3} mmol/day at the 25^{th} percentile level. Overall, for the first time, this research has developed thresholds of toxicological concern based on molecular structure of chemicals, to enable screening-level occupational risk assessment and prioritization in data poor situations.

Keywords: Occupational Exposure Limit, Threshold of Toxicological Concern, physiologically based pharmacokinetic modeling, quantitative property-property relationships, occupational health risk assessment.

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Liste des sigles

ACGIH	American Conference of Governmental Industrial Hygienists
CMP	Chemical Management Plan
DFG	Deutsche Forschungsgemeinschaft
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
HSE	Health and Safety Executive
NIOSH	National Institute for Occupational Safety and Health
NSERC	Natural Sciences and Engineering Research Council of Canada
OSHA	Occupational Safety and Health Administration
PGPC	Plan de gestion des produits chimiques
SCOEL	Scientific Committee for Occupational Exposure Limits
WHO	World Health Organization

Liste des abréviations

3R	réduction, raffinement, remplacement
AUC	aire sous la courbe de concentration en fonction du temps (*area under the concentration versus time curve*)
AD	domaine d'application
ANOVA	analyse de variance (*analysis of variance*)
BW	poids corporel
BMD (ou BMC)	dose ou concentration de référence (*Benchmark Dose/or Concentration*)
C	concentration (f, l, r, s, t en indice pour : tissu adipeux, foie, tissus richement perfusés (ou reste du corps selon le cas), tissus faiblement perfusés (ou peau et muscles selon le cas), tissu)
c.-à-d.	c'est-à-dire
CA (ou Ca)	concentration artérielle
C_{avl}	concentration alvéolaire
CAS (ou CASRN)	numéro d'identification de la substance, attribué par l'American Chemical Society (*Chemical Abstract Service/Register Number*)
C_{inh}	concentration inhalée
CL_h	clairance hépatique
CL_{int}	clairance intrinsèque
CMAX	concentration maximale
CV (ou C_v)	concentration veineuse (f, l, r, s, t en indice pour : tissu adipeux, foie, tissus richement perfusés (ou reste du corps selon le cas), tissus faiblement perfusés (ou peau et muscles selon le cas), tissu)
CYP	cytochrome P450
dA/dt	taux de changement de la quantité de substance
dA_m/dt	taux de changement de la quantité de substance métabolisée
df	degré de liberté
DL_{50}	Dose létale 50
E	ratio d'extraction hépatique
Exp	expérimental(e)

FI	Facteur d'incertitude (ou de sécurité)
F_{nle}	fraction volumétrique d'équivalents en lipides neutres
F_{we}	fraction volumétrique d'équivalents en eau
g	gramme
GM	moyenne géométrique
GSD	déviation standard géométrique
H (ou hr)	heure
HTP	à haut débit (*high-throughput*)
IVIVE	extrapolation *in vitro-in vivo*
K_{el}	constante d'élimination de premier ordre
Kg	kilogramme
K_m	constante d'affinité de Michaelis-Menten
L (ou l)	litre
Log	logarithme de base 10
m^3	mètre cube
MAK	Maximale Arbeitsplatz-Konzentration
Max	maximum ou maximal(e)
MBDE	équation différentielle de masse (*mass-balance differential equation*)
Med	médiane
mg	milligramme
Min	minimum ou minimal(e)
mol	mole
mmole	millimole
MW	masse moléculaire
NO(A)EL	dose maximale sans effet (néfaste) observé (*No observed (adverse) effect level*)
OEB	bande d'exposition professionnelle (*Occupational Exposure Banding*)
OEL	valeur limite d'exposition professionnelle (*Occupational Exposure Limit*)
OTTC	seuil de préoccupation toxicologique pour l'exposition professionnelle (*Occupational Threshold of Toxicological Concern*)
p. ex.	par exemple

Pa	Pascal
P_{aw}	coefficient de partage air:eau
P_{ba}	coefficient de partage sang:air
P_{oa}	coefficient de partage *n*-octanol:air
P_{ow}	coefficient de partage *n*-octanol:eau
P_{ta}	coefficient de partage tissu:air (t pouvant prendre les valeurs f, l, r, s pour : tissu adipeux, foie, tissus richement perfusés (ou reste du corps selon le cas), tissus faiblement perfusés (ou peau et muscles selon le cas))
P_{tb}	coefficient de partage tissu:sang (t pouvant prendre les valeurs f, l, r, s pour : tissu adipeux, foie, tissus richement perfusés (ou reste du corps selon le cas), tissus faiblement perfusés (ou peau et muscles selon le cas))
P_{voa}	coefficient de partage huile (végétale):air
P_{vow}	coefficient de partage huile (végétale):eau
PBPK	pharmacocinétique à base physiologique (*Physiologically Based Pharmacokinetic*)
PC	physico-chimique
PHB	biphényles polyhalogénés (*Polyhalogenated Biphenyls*)
POD	point de départ (*Point of Departure*)
ppm	parties par million
Pred	prédit(e)
PRF	facteur de rétention pulmonaire
QC (ou Q_c)	débit cardiaque
QP (ou Q_p)	ventilation alvéolaire
Q_t	débit sanguin du tissu t correspondant (t pouvant prendre les valeurs f, l, r, s pour : tissu adipeux, foie, tissus richement perfusés (ou reste du corps selon le cas), tissus faiblement perfusés (ou peau et muscles selon le cas))
QPPR	relation quantitative propriété-propriété (*Quantitative Property-Property Relationship*)
QSAR	relation quantitative structure-activité (*Quantitative Structure-Activity Relationship*)

QSPR	relation quantitative structure-propriété (*Quantitative Structure-Property Relationship*)
RAM (ou RMET)	taux de quantité de substance métabolisée pendant une période de temps spécifié
SC	coefficient de sensibilité
SD	déviation standard
SST	santé et sécurité au travail
STEL	limite d'exposition court terme (*Short Term Exposure Limit*)
T (ou t)	durée d'exposition
TLV	valeur limite d'exposition professionnelle recommandée par l'ACGIH (*Threshold Limit Value*)
TTC	seuil de préoccupation toxicologique (*Threshold of Toxicological Concern*)
TWA	moyenne pondérée dans le temps (*Time-Weighted Average*)
µg	microgramme
V	taux de ventilation pulmonaire
V_b	volume de sang
V_d	volume de distribution
V_{max}	vitesse maximale du métabolisme
V_t	volume du tissu t correspondant (t pouvant prendre les valeurs f, l, r, s pour : tissu adipeux, foie, tissus richement perfusés (ou reste du corps selon le cas), tissus faiblement perfusés (ou peau et muscles selon le cas))
VLEP	valeur limite d'exposition professionnelle (*Occupational Exposure Limit* en anglais)
VP	pression de vapeur
WS	solubilité dans l'eau

Le savoir n'a pas de prix; il constitue une richesse qui procure une fierté incommensurable.

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Introduction générale

Les travailleurs inhalent les substances chimiques qui se retrouvent dans l'air ambiant de leurs milieux de travail. Cette exposition professionnelle pourrait initier des dérèglements au niveau des organes ou fonctions physiologiques, résultant en des problèmes de santé de divers ordres. Ainsi, pour évaluer l'exposition des travailleurs aux contaminants de l'air ambiant de leurs lieux de travail et ultimement caractériser et gérer les risques sanitaires y étant associés, des valeurs limites d'exposition professionnelle (VLEP[1]), qui sont des niveaux de concentrations atmosphériques à ne pas dépasser, sont établies.

En général, les substances chimiques peuvent être classées en deux catégories : celles possédant des données de toxicité adéquates pour développer une valeur limite d'exposition et celles n'en possédant pas. Cependant, du fait d'un nombre important de substances chimiques (habituellement celles de la 2^{e} catégorie de substances) auxquelles ne sont associées aucune valeur de référence, plusieurs solutions de rechange, dont particulièrement les approches dites qualitatives, ont été développées. C'est notamment le cas des approches basées sur le concept de bandes de dangerosité dont les plus connues sont: le « *Control Banding* » et l'« *Occupational Exposure Banding* - OEB » (NIOSH, 2017). Bien que la stratégie de l'OEB soit de plus en plus rapportée dans la littérature grise (p. ex. le magazine « the Synergist » de l'AIHA – *American Industrial Hygiene Association*), celle du « *Control Banding* » est la plus connue et utilisée en milieu de travail (Scheffers et al., 2016). Elle a été initiée à la fin des années 1980 dans l'industrie pharmaceutique pour outiller les petites et moyennes entreprises n'ayant pas les ressources et l'expertise nécessaire pour développer des stratégies de contrôle de l'exposition de leurs employés aux substances n'ayant pas de données de toxicité (p. ex. les ingrédients pharmaceutiques actifs) (Farris, Ader et Ku, 2006; Naumann et al., 1996). De nos jours, l'approche est largement appliquée dans le domaine de la santé et sécurité au travail (SST) et connait de vifs succès avec les outils tels que le « *Control of Substances Hazardous to Health* -

[1] Dans le contexte de cette thèse, le terme VLEP réfère à l'acronyme anglais *OEL (Occupational Exposure Limit)* et sous-entend donc des seuils d'exposition développés pour évaluer et gérer l'exposition des travailleurs aux contaminants de l'air de leur milieu de travail.

COSHH Essentials » du Royaume Uni (HSE, 2002) ou le « *Control Banding* » du « NIOSH - *National Institute for Occupational Safety and Health* » des États-Unis (NIOSH, 2009). Par ailleurs, le concept d'« hiérarchie de VLEP » est de plus en plus mentionné dans la littérature grise. Ce concept consiste en un organigramme structuré pour guider les professionnels de SST dans un choix éclairé et justifiable des approches à préconiser pour l'évaluation des risques des substances, en fonction de la disponibilité des données sur leur toxicité (Deveau et al., 2015; Laszcz-Davis, Maier et Perkins, 2014; O'Malley et Roy, 2014). Le concept intègre toutes les approches disponibles, quantitatives et qualitatives, dans une pyramide; les approches situées dans le bas de la pyramide étant celles nécessitant le moins de ressources et associées aux incertitudes les plus élevées dans la caractérisation des risques. Cette hiérarchisation des approches et outils permet une meilleure intégration de tous ceux disponibles dans la *boite à outils* des professionnels en SST, pour la surveillance, l'évaluation et le contrôle de l'exposition des travailleurs.

Malgré l'utilité et le pragmatisme des approches qualitatives et semi-quantitatives, celles-ci ne sauraient remplacer l'analyse quantitative du risque, c.-à-d. la dérivation quantitative des VLEP pour les contaminants de l'air en milieu professionnel (Henschler, 1991). Ainsi, soustraire la démarche quantitative pourrait causer un manque de données empiriques sur la toxicité des substances (p. ex. épidémiologiques ou d'expérimentations animales), pourtant nécessaires pour valider les approches (qualitatives et semi-quantitatives) proposées (Borak et Brosseau, 2015). Aussi, les VLEP sont nécessaires pour valider les stratégies de contrôle de l'exposition (Brandys et Brandys, 2008). D'où la pertinence de maintenir l'évaluation quantitative du risque et plus spécifiquement l'importance de l'évaluation quantitative de l'exposition, laquelle est basée sur les VLEP.

La VLEP, sujet principal de cette recherche et de cette thèse, est un concept large et complexe. Dans le cadre de cette recherche, une attention particulière a été accordée à la compréhension des divers processus utilisés pour l'établir. La revue de littérature porte essentiellement sur les approches conceptuelles utilisées pour la dérivation quantitative de VLEP pour des substances chimiques organiques induisant des effets sanitaires dits déterministes, encore appelées substances à seuil de toxicité ou substances à seuil. Il s'agit de substances possédant un seuil de dose ou concentration en deçà duquel aucun effet néfaste

(significatif) n'est anticipé. Par ailleurs, les données de littérature indiquent que près de 50% des VLEP sont basées sur les effets systémiques et environ 40% sur l'irritation (p. ex. des yeux ou des voies respiratoires supérieures) (Brüning et al., 2014; Jakubowski et Czerczak, 2010; Kuwabara, Alexeeff, Broadwin et Salmon, 2007; Nielsen, Wolkoff et Alarie, 2007; Paustenbach, Cowan et Sahmel, 2011). Cette dichotomie a donc été considérée lors de la revue de littérature et les résultats de celle-ci sont donc présentés dans la présente thèse en fonction de la nature de l'effet (c.-à-d. irritant ou systémique) et de l'adéquation des données de toxicité des substances.

Organisation de la thèse

Bien que les VLEP soient développées et établies pour une panoplie d'agents chimiques pouvant être retrouvés dans l'air ambiant des lieux de travail, la présente thèse ne s'intéresse qu'aux substances chimiques organiques à seuil de toxicité ou substances systémiques à effets déterministes.

Cependant, être en mesure de développer des approches quantitatives pour la prédiction de VLEP nécessite la compréhension préalable du concept de VLEP dans son intégrité. Ainsi, le chapitre 1 brosse un portrait du concept de VLEP (définition, applications en milieu de travail et les différents types). Par la suite, est documenté un état des connaissances scientifiques sur les approches quantitatives qui existent pour développer et établir les VLEP de substances chimiques organiques. Le chapitre 2 dresse en quelque sorte la table en mettant en contexte la recherche proprement dite et réalisée dans le cadre de cette thèse. Ainsi, la problématique du sujet de recherche y est présentée suivie des principaux objectifs de recherche, lesquels sont abordés séquentiellement dans les chapitres 3 à 5. Le chapitre 3 présente une approche permettant de développer des seuils de préoccupation toxicologique (c.-à-d. des valeurs limites provisoires) pour l'exposition professionnelle. Il est à souligner que les travaux relatifs à cette section de la recherche ont abouti à la publication d'un article qui a été sélectionné comme meilleur article de l'année 2017 par les pairs de la sous-section « *Occupational and Public Health Specialy Section* » de la « *Society of Toxicology* ». Le chapitre 4 quant à lui propose un cadre structuré pour la modélisation toxicocinétique intégrée et à haut débit. Il s'agit d'un cadre de modélisation à base physiologique permettant la prédiction de la toxicocinétique et des doses

internes de centaines de substances en temps réel, en utilisant principalement l'information sur leur structure moléculaire. Dans le chapitre 5, le cadre d'analyse proposé au chapitre 4 est utilisé pour prédire des doses internes. Ces dernières sont alors utilisées pour : i) proposer des seuils de préoccupation toxicologique pour l'exposition professionnelle qui sont basés sur la dose interne; ii) explorer la relation quantitative qui existe entre dose interne et VLEP, permettant de développer des modèles quantitatifs et prédictifs des valeurs limites provisoires pour l'exposition professionnelle. Finalement une discussion générale des principales contributions et limites majeures de la recherche est présentée au chapitre 6, suivie d'une conclusion générale.

Chapitre 1. Revue de littérature portant sur le développement des VLEP de substances organiques non cancérigènes

1.1. Concept de valeur limite d'exposition professionnelle

1.1.1. Définition et objectifs

La valeur limite d'exposition professionnelle (VLEP) est un concept vaste dont la définition exacte et les fondements spécifiques varient en fonction de l'instance (p. ex, organisme réglementaire) qui la développe. Cependant, d'un point de vue conceptuel, la VLEP d'une substance chimique pourrait être définie comme étant sa concentration maximale dans l'air ambiant du milieu de travail à laquelle les travailleurs pourraient être exposés par inhalation dans des conditions données (p. ex. sur une période de référence déterminée) sans risque significatif d'effets sanitaires potentiellement nocifs (EC, 2013; ECETOC, 2006; Henschler, 1991; Howard, 2005).

Fondamentalement, une VLEP constitue un instrument; par instrument, on sous-entend un moyen. Ainsi, la VLEP d'une substance a pour objectif de permettre l'évaluation et le contrôle de l'exposition des travailleurs à celle-ci, et par le fait même, la prévention, la caractérisation et la gestion des risques sanitaires potentiels qui pourraient résulter de cette exposition (Borak et Brosseau, 2015; Henschler, 1991; Howard, 2005).

1.1.2. Applications et utilisations

Les VLEP sont donc des valeurs de référence développées à travers le monde afin de guider les professionnels de SST dans la prise de décisions relatives à l'exposition des travailleurs aux substances chimiques inhalables. Ainsi, ces valeurs demeurent des instruments essentiels et tangibles, malgré la remise en question perpétuelle de leur efficience réelle (Howard, 2005). Les VLEP devraient idéalement être utilisées et interprétées par un personnel qualifié (p. ex. hygiéniste, toxicologue, médecin de santé au travail) (ACGIH, 2016; Howard, 2005; Nielsen et Øvrebø, 2008; Vincent, 1998). Signe de leur utilité, elles constituent des outils fondamentaux et stratégiques de prévention primaire en santé publique. Plus spécifiquement, elles sont utilisées notamment pour l'évaluation et le contrôle de l'exposition des travailleurs, la caractérisation et la gestion des risques sanitaires potentiels qu'ils pourraient encourir à la suite de leur surexposition par inhalation aux substances chimiques présentes dans l'air ambiant de leur environnement professionnel (ACGIH, 2016; EC, 2013; ECETOC, 2006; Gordon et al.,

2014; HSE, 2011; Walters, Grodzki et Walters, 2003). Ainsi, du fait de sa nature quantitative, la VLEP d'une substance sera utilisée comme sa valeur atmosphérique de référence pour évaluer l'exposition des travailleurs. Dans la pratique donc, celle-ci sera utilisée comme étalon auquel seront comparées les données estimées ou de mesurage de l'exposition des travailleurs à ladite substance, afin de juger de l'acceptabilité de leur exposition (p. ex. leur conformité aux normes) et de caractériser leurs risques sanitaires potentiels (Waters et al., 2015; Whaley, Attfield, Bedillion, Walter et Yi, 2000). Un exemple concret de caractérisation du risque est le calcul du quotient de danger qui est très utile pour estimer l'ordre de grandeur de la différence entre les données d'exposition mesurées (ou estimées) d'une substance et la valeur de sa VLEP correspondante (Debia, Begin et Gerin, 2011; Waters et al., 2015). Soulignons que ces comparaisons doivent se faire dans des contextes bien précis; par exemple, les données de mesure doivent être pondérées dans le temps avant d'être comparées avec les VLEP-8h ou VLEP-15 min, selon le cas (Whaley et al., 2000).

Les VLEP constituent aussi des composantes essentielles du cadre de gestion du risque en milieu professionnel; du moins, elles le devraient pour la plupart des (grandes) entreprises (Howard, 2005). Ainsi, elles permettent aux gestionnaires d'estimer les marges d'exposition et/ou de sécurité relatives aux expositions préoccupantes (Hansson et Rudén, 2006). De plus, elles sont parfois considérées lors de la prise de décisions relatives aux stratégies de surveillance de l'air et de contrôle de l'exposition (p. ex. efficacité des procédures techniques, identification des procédures nécessitant des mesures de contrôle, port d'équipements de protection personnelle, implantation de bonnes pratiques) (Henschler, 1991; Howard, 2005; Waters et al., 2015). En outre, elles servent lorsque vient le temps de faire des recommandations à des fins d'ingénierie comme par exemple lors de la conception d'instruments de mesure ou de procédures, tous permettant l'échantillonnage de l'atmosphère des lieux de travail (ACGIH, 2016; EC, 2013; ECETOC, 2006; Mulhausen, Damiano et Pullen, 2006).

Il est cependant essentiel de souligner que les VLEP ne devraient pas être utilisées pour juger de la sécurité d'une exposition (car p. ex. plusieurs substances de toxicités différentes peuvent avoir une même VLEP), pour comparer la toxicité des substances, à des fins diagnostiques et encore moins pour caractériser les risques environnementaux (ACGIH, 2016; EC, 2013; Nielsen et Øvrebø, 2008; Roach et Rappaport, 1990; Vincent, 1998).

1.1.3. Types de VLEP selon les données sur lesquelles elles sont basées

De façon générale, en milieu de travail, il existe deux types de valeurs de référence qui diffèrent selon qu'elles soient développées sur la base de considérations sanitaires uniquement ou non: les VLEP recommandées et les VLEP réglementaires (Austin, 2004; ECETOC, 2006; Mulhausen et al., 2006; Paustenbach et al., 2011; Waters et al., 2015).

La **VLEP recommandée** d'une substance chimique est une estimation du niveau de celle-ci dans l'air ambiant du milieu de travail en-dessous duquel il est vraisemblable qu'aucun effet sanitaire nocif significatif ne se manifestera chez *presque tous* les travailleurs (et leur progéniture), et ce, suite à des expositions quotidiennes durant leur vie professionnelle (ACGIH, 2016; EC, 2013; ECETOC, 2006). Concrètement, cette définition fait référence uniquement à des disfonctionnements apicaux tels que des dérèglements d'organes ou atteintes fonctionnelles graves, vu que certains effets physiologiques peuvent parfois être transitoires et réversibles (ACGIH, 2016; ANSES, 2017; EC, 2013; ECETOC, 2006; HSE, 2011; Triebig, 2002; Vincent, 1998; Walters et al., 2003). Ainsi, les VLEP recommandées sont *réputées* être basées uniquement sur des critères sanitaires en considérant les données de toxicité les plus pertinentes au moment de l'évaluation des substances d'intérêt. Quoique, les données de littérature indiquent qu'en réalité, certaines d'entre elles tiennent aussi très souvent compte de la faisabilité technique (Deveau et al., 2015).

Ces valeurs limites sont très souvent recommandées par des comités (réputés indépendants) d'experts scientifiques aux compétences variées et complémentaires au sein d'institutions indépendantes, agences gouvernementales, organismes publics ou d'organisations professionnelles, internationalement reconnus. Parmi celles-ci, on peut citer les « TLV® - *Threshold Limit Values* » de l'*American Conference on Governmental Industrial Hygienists* (ACGIH®, États Unis), les « WEEL® - *Workplace Environmental Exposure Levels* » de l'*Occupational Alliance for Risk Science* (OARS, États Unis), les « REL - *Recommended Exposure Limits* » du *National Institute for Occupational Safety and Health* (NIOSH, États Unis), les « IOELV - *Indicative OEL Values* » recommandées par le *Scientific Committee on Occupational Exposure Limits* (SCOEL, Union Européenne) à la Commission Européenne, les « MAK - *Maximale Arbeitsplatz-Konzentration*» *du German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area* (DFG, Allemagne).

Bien que plusieurs agences et instances mondiales recommandent des VLEP, notamment pour les gaz, vapeurs et aérosols de contaminants de l'air en milieu de travail (Brandys et Brandys, 2008; Nielsen et Øvrebø, 2008; Skowroń et Czerczak, 2015; Vincent, 1998; Walters et al., 2003), seules les TLV® recommandées par l'ACGIH® jouissent d'une notoriété mondiale et sont même très souvent considérées par d'autres instances lors du développement de leurs propres VLEP (Hansson et Rudén, 2006; Vaughan et Rajan-Sithamparanadarajah, 2017; Vincent, 1998). L'ACGIH® publie annuellement une mise à jour des TLV® qui sont de 3 types: 8-hour TLV®-TWA (*Time-Weighted Average*), 15-min TLV®-STEL (*Short-Term Exposure Limit*) et C (*Ceiling*), pour VLEP-8h, VECT-15min et VP, respectivement.

Les **VLEP réglementaires** sont des valeurs limites (contraignantes) ayant force de loi. Plus spécifiquement, il s'agit de normes (le plus souvent nationales) qui sont en général le fruit de la réglementation des VLEP recommandées par les instances gouvernementales. Ainsi, en plus des critères sanitaires (du fait des VLEP recommandées qui en constituent le point focal), ces VLEP réglementaires intègrent aussi des considérations techniques, analytiques, socio-économiques, politiques, et même légales (ECETOC, 2006), de telle sorte qu'elles constituent généralement des valeurs légalement contraignantes enchâssées dans des politiques nationales. C'est ce qui explique les variations très souvent observées d'une juridiction à une autre, par exemple, dans leurs définitions, les démarches pour leur développement et leurs applications (Austin, 2004; Vincent, 1998; Walters et al., 2003). Il peut cependant arriver qu'une substance ait des valeurs de ses VLEP recommandée et réglementaire équivalentes; ceci ne saurait affecter le statut légal de la dernière. Dans cette catégorie de VLEP, nous pouvons citer les « PEL - *Permissible Exposure Limits* » promulguées par l'*Occupational Safety and Health Administration* (OSHA, États-Unis), les « *Binding OEL* » de l'Union Européenne (EC, 2013; HSE, 2011; Paustenbach et al., 2011; Vincent, 1998).

Cependant dans la réalité, bon nombre de contaminants de l'air en milieu de travail ne possèdent pas de VLEP. Pourtant, les employeurs sont généralement tenus de contrôler l'exposition de leurs employés, d'évaluer et/ou prévenir les risques sanitaires qui pourraient résulter de leur surexposition aux agents chimiques présents dans l'atmosphère de leurs lieux de travail. Ainsi, lorsqu'aucune des valeurs de référence (recommandées ou réglementaires) discutées précédemment n'existent, de plus en plus d'entreprises établissent elles-mêmes des

valeurs limites appelées **VLEP internes** ou encore **VLEP d'entreprises,** en plus des solutions qualitatives et semi-quantitatives rapportées dans la littérature. Ces valeurs sont généralement établies par des comités d'entreprises ou de compagnies, pour gérer des situations dans lesquelles aucune autre valeur limite (recommandée ou réglementaire) n'existe ou alors que l'information ayant servie à leur développement n'est plus pertinente, permettant ultimement de protéger leurs employés, et même leurs clients (Mulhausen et al., 2006; Paustenbach et al., 2011). Ces VLEP sont construites à partir des mêmes types de données et suivant les mêmes approches que celles utilisées pour établir les VLEP recommandées ou réglementaires. Cependant, dans une telle situation un avantage important qu'ont les compagnies/entreprises pour développer des VLEP internes réside, entre autres, dans leur accessibilité aux données d'exposition et de surveillance médicale de leurs travailleurs. En revanche, la nécessité de ressources (financières et humaines entre autres) considérables du fait des coûts associés au développement d'une VLEP peut constituer un inconvénient majeur. (ECETOC, 2006; Paustenbach et Langner, 1986).

Il existe aussi les **VLEP provisoires (ou *working OEL*).** Il s'agit de seuils intérimaires et informels établis pour des substances (très) peu étudiées ayant des données de toxicité très limitées sinon inexistantes, permettant une évaluation de l'exposition des travailleurs lorsqu'aucune autre valeur limite n'existe. Elles sont généralement estimées sur la base d'une comparaison par analogie structurelle entre les substances sans VLEP et celles qui en possèdent (EC, 2013; ECETOC, 2006; Mulhausen et al., 2006). Il s'agit d'outils permettant au minimum de sélectionner des substances d'intérêt ou à prioriser dans un contexte où les données de toxicité sont limitées. À noter que, le qualificatif « provisoire » ne devrait être perçu comme réducteur mais plutôt comme une indication de l'attention particulière que requiert leur utilisation et l'interprétation des niveaux d'exposition. En effet, leur élaboration implique souvent des facteurs d'incertitude considérables dû aux lacunes des bases de données toxicologiques (ECETOC, 2006; Mulhausen et al., 2006).

1.1.4. Types de VLEP selon le profil toxicologique des substances

Une VLEP ne s'applique qu'à la voie respiratoire et est habituellement développée pour des substances chimiques individuelles (EC, 2013; Nielsen et Øvrebø, 2008). Cela dit, qu'elle

soit recommandée, réglementaire ou autre, elle est établie sous forme de moyenne pondérée dans le temps, en fonction du profil toxicologique de la substance d'intérêt. Ainsi, on en recense principalement trois types : la valeur d'exposition moyenne pondérée (VEMP), la valeur limite court-terme (VLCT) et la valeur plafond (VP).

La VEMP est la concentration moyenne d'une substance chimique dans l'atmosphère résidant au niveau de la zone respiratoire du travailleur et qui est pondérée sur un horaire de travail conventionnel. Ce dernier est généralement considéré comme étant de huit heures par jour, 40 heures par semaine, d'où la VEMP sur 8 heures ou VLEP-8h. Il s'agit de l'expression la plus courante de VLEP qui est destinée à protéger les travailleurs des effets sanitaires pouvant survenir à long ou moyen termes à la suite d'une surexposition quotidienne leur vie professionnelle durant. Si l'analyse du profil toxicologique de la substance le supporte, une VLCT, généralement pondérée sur une période de référence de 15 minutes (d'où VLCT-15 min), peut aussi être établie pour protéger des effets induits par les expositions aiguës et répétées (p. ex. irritation, perte de conscience) ou des pics d'exposition (sans égard à leur durée) qui ne pourraient être prévenus par la VMEP. Soulignons que des ajustements de ces valeurs sont requis pour des horaires dits non conventionnels (ANSES, 2017; Drolet, 2015; Henschler, 1991).

Par ailleurs, la VLEP-8h peut être dépassée pendant de courtes périodes de temps au cours de la durée de travail de 8 heures à condition de ne pas dépasser la VLCT-15 min lorsqu'elle existe. Cependant, pour les substances possédant une VLEP-8h mais pas de VLCT-15 min, des limites d'excursion sont permises. Ainsi, tant et aussi longtemps que la VLEP-8h n'est pas excédée, des dépassements supérieurs à 3 fois la VLEP-8h mais inferieurs à 5 fois celle-ci pendant 15 minutes chaque sont tolérés, et ce, pour une période cumulée maximale de 30 minutes durant le quart de travail de 8 heures par jour. Il existe aussi des VP qui ne doivent jamais être dépassées durant le quart de travail de 8 h. Ces valeurs ont pour but de protéger les travailleurs d'effets sanitaires néfastes qui ne pourraient être prévenus par l'application unique des VLEP-8 h et/ou VLCT-15 min (ACGIH, 2016; Austin, 2004; EC, 2013; ECETOC, 2006; HSE, 2011; Paustenbach et al., 2011).

Pour les gaz et vapeurs, les VLEP sont généralement exprimées en parties par million (ppm) ou en milligramme de substance par mètre cube d'air (mg/m^3). Si la pertinence a été

démontrée, les VLEP établies peuvent être accompagnées de mentions signalant d'autres caractéristiques de la substance telles qu'une contribution significative de l'absorption cutanée (c.à.d. plus de 10% de ce qui est inhalé) à la charge corporelle totale (mention « peau »), le pouvoir cancérigène ou sensibilisant, par exemple. Par ailleurs, il est à noter que, vu que les VLEP ne s'appliquent qu'à l'inhalation, une évaluation de l'exposition par les autres voies potentielles (p. ex., les voie orale et/ou cutanée) peut le cas échéant être nécessaire pour une évaluation du risque sanitaire global des travailleurs (ACGIH, 2016; EC, 2013).

En définitive, on dira que le concept de VLEP en est un qui englobe en plus de la valeur de VLEP proprement dite, le temps moyen d'exposition et les attributs de la population d'intérêt (c.à.d. jeunes travailleurs en bonne santé entre autres) auxquels elle s'applique (ANSES, 2017).

1.2. Établissement de VLEP pour substances avec données de toxicité adéquates

Les VLEP recommandées et réglementaires sont des VLEP publiques. Les VLEP réglementaires tiennent compte des aspects sanitaires en plus des considérations socio-économiques et de la faisabilité technique; et comme mentionné plus haut, les VLEP internes se basent sur les mêmes approches que les VLEP recommandées, mis à part qu'elles sont propres aux compagnies et entreprises. Ainsi, le lecteur est avisé que la revue porte sur les approches pour développer des VLEP recommandées, réputées essentiellement basées sur des considérations sanitaires. Cependant, par souci de clarté, seule l'expression VLEP sera utilisée dans les sections suivantes de ce document.

La publication d'une approche conceptuelle unique et harmonisée pour la dérivation quantitative de VLEP pour des substances ayant des données de toxicité adéquates continue de susciter le débat scientifique (Illing, 1991; Lundberg, 1994; Maier et al., 2015). Néanmoins, une observation minutieuse des monographies accompagnant ces valeurs indique : i) qu'elles sont développées et établies pour des substances individuelles; ii) que le processus de leur développement s'amorce par une évaluation de toutes les données de toxicité (provenant p. ex. d'études épidémiologiques (comprenant les études expérimentales chez des volontaires) disponibles, de la surveillance des travailleurs, ou alors d'études expérimentales chez les

animaux); et iii) que de plus en plus, les données de toxicité dérivées d'études expérimentales chez les animaux en constituent la base (Vincent, 1998). Ainsi, cette évaluation des données de toxicité qui se matérialise par l'analyse et le résumé des effets sanitaires et toxicologiques suivis du choix des études les plus pertinentes, a pour but d'établir le profil toxicologique de la substance étudiée : c'est-à-dire la caractérisation de son potentiel de dangerosité et ultimement, celle de sa relation dose (ou concentration) d'exposition/réponse (ou effet). Par souci de clarté, nous utiliserons seulement l'expression dose/réponse dans la suite du document.

La caractérisation du potentiel de dangerosité d'une substance est essentiel pour l'établissement du profil toxicologique d'une substance et pour le choix de l'approche d'analyse du risque à adopter pour l'estimation quantitative d'une VLEP : *approche déterministe* pour les substances ayant un seuil de toxicité ou *approche probabiliste* pour celles n'ayant pas de seuil (p. ex. cancérigènes génotoxiques) (EC, 2013; ECETOC, 2006; Nielsen et Øvrebø, 2008; Paustenbach et al., 2011; Pechacek, Osorio, Caudill et Peterson, 2015; Vincent, 1998). Dans ce dernier cas, l'approche par défaut est celle de l'estimation d'un excès de risque et des modèles mathématiques d'extrapolation aux faibles doses (p. ex multistage, one/multi-hit, Weibull) sont couramment utilisés (Nielsen et Øvrebø, 2008; Paustenbach et al., 2011).

Pour les substances à effets déterministes (encore dites substances à seuil), sujet de cette thèse, l'hypothèse à la base de cette approche est que la relation dose/réponse est caractérisée par l'existence d'un seuil de dose (ou concentration) sous lequel l'exposition n'induira pas d'augmentation significative d'effets néfastes (Nielsen et Øvrebø, 2008) et ce, pour la majorité des travailleurs. Ainsi, la caractérisation de cette relation dose/réponse permettra l'identification de ce seuil de toxicité ou dose critique ou point de départ. Ce dernier, mieux connu sous la dénomination « POD - *point of departure* », constitue le point focal de l'extrapolation quantitative de la relation dose/réponse en VLEP.

L'approche utilisée par défaut pour cette extrapolation est celle de l'agence américaine de protection de l'environnement (l'*U.S. Environmental Protection Agency* ou *U.S. EPA*) pour l'établissement des doses ou concentrations de référence (*RfD* et *RfC* respectivement) pour des expositions environnementales (EPA, 1994, 2002; WHO, 1994). Conceptuellement, celle-ci se fonde sur l'utilisation du POD et l'application dans le calcul de facteurs d'incertitude (Brüning

et al., 2014; Dankovic, Naumann, Maier, Dourson et Levy, 2015; Gould, Kasichayanula, Shepperly et Boulton, 2013; Poet et al., 2010; Skowroń et Czerczak, 2015).

1.2.1. Concept de facteur d'incertitude

Les facteurs d'incertitude (FI), souvent appelés facteur de sécurité, permettent de considérer les diverses incertitudes et variabilités dans les données lors des extrapolations de la démarche d'analyse de risque. On en recense plusieurs comme par exemple pour : la variabilité inter-espèce, la variabilité inter-individuelle (état de santé, âge, génétique), l'utilisation de la LO(A)EL au lieu de NO(A)EL, extrapolation d'exposition sous-chronique à chronique, les lacunes de la base de données. Bien que les valeurs par défaut de chacun de ces FI soient en général égales à 10, dans la réalité, celles-ci dépendent fortement du jugement d'experts.

1.2.1.1. Substances irritantes

Pour les substances irritantes, les FI sont habituellement inférieurs à la valeur par défaut de 10 (p. ex., chlore, formaldéhyde). Les justifications étant entre autres que: le lapin est plus sensible que l'humain, l'irritation (sensorielle) est en général transitoire ou réversible, ou encore les comités en charge de dériver des VLEP ont généralement accès à de grosses bases de données empiriques d'exposition des travailleurs (Paustenbach et al., 2011; Skowroń et Czerczak, 2015). Ainsi par exemple, selon le jugement des experts, une valeur de 1 ou 3 est généralement attribuée au FI pour l'extrapolation inter-espèce; généralement 1 (mais souvent 3 ou 5 selon la pertinence des données) pour l'extrapolation inter-individuelle (ANSES, 2017). Aussi, des valeurs variant de 2 à 5 ont été rapportées pour l'extrapolation de LO(A)EL à NO(A)EL (Alexeeff, Broadwin, Liaw et Dawson, 2002).

1.2.1.2. Substances à effets systémiques

Lorsqu'on dispose des données épidémiologiques, un FI variant de 1 à 3 est généralement utilisé pour la variabilité inter-individuelle, pour un maximum de 5 car une population de travailleurs est plus homogène que la population générale (ANSES, 2017; Frangos, Mikkonen et Down, 2016; Maier, Kohrman-Vincent, Parker et Haber, 2010).

Cependant, la nature et la valeur des FI peuvent varier, entre autres, selon l'instance développant les VLEP, l'effet (critique sélectionné) ou la constitution de la base de données de toxicité. Dès lors, les valeurs de FI sont constamment remises en question dans la communauté scientifique (Dankovic et al., 2015; Dourson et Stara, 1983; Schenk et Johanson, 2010, 2018). Ainsi, un facteur d'ajustement spécifique à la substance chimique ou « CSAF - *chemical specific adjustment factor* » est de plus en plus recommandé et privilégié si les données le permettent (Dankovic et al., 2015; WHO, 2010). Pour ce faire, ces dernières décennies, plusieurs solutions de rechange ont été proposées pour permettre le calcul du CSAF et ainsi réduire les valeurs par défaut des FI. Il s'agit, entre autres, de la modélisation pharmacocinétique (Gould et al., 2013; Pastino, Kousba, Sultatos et Flynn, 2003; Pemberton, Bailey et Rhomberg, 2013; Poet et al., 2010; Sweeney et al., 2001) et des systèmes biologiques (DeBord et al., 2015; Kuempel, Sweeney, Morris et Jarabek, 2015). Ainsi, Kuempel et al. (2015) ont utilisé l'exemple du dioxyde de titanium (TiO_2) pour appuyer l'utilité des modèles biologiques, basés sur le concept de dosimétrie (mesure or estimation de la dose inhalée), pour réduire l'incertitude associée à l'estimation de la dose à l'organe cible, c.-à-d., celle associée à l'effet lors de la dérivation des VLEP. Par ailleurs, dans leur exposé, DeBord et al. (2015) discutent aussi des avantages et limites de l'utilisation de biomarqueurs d'effet (et des modèles biologiques) pour préciser le calcul des VLEP.

1.2.2. Concept de point de départ

Le POD équivaut à la dose associée à l'effet (bio-pathologique) le plus sensible ou *effet critique* identifié dans l'étude clé sélectionnée lors de l'établissement du profil toxicologique de la substance (ACGIH, 2016; Nielsen et Øvrebø, 2008; Paustenbach et al., 2011). Basé sur des données empiriques, le POD peut être ajusté pour tenir compte entre autres de : la durée d'exposition (p. ex. pour les VLCT), la biodisponibilité de la substance d'intérêt chez l'espèce d'intérêt ou la voie d'exposition, la dosimétrie différente entre les espèces, des caractéristiques de la sous-population d'intérêt qui est celle des travailleurs (p. ex. population homogène de jeunes individus en bonne santé ayant un poids moyen; volume respiratoire (activité versus repos); exposition moyenne de 8 heures /jour, 40 heures /semaine; durée maximale d'exposition professionnelle d'environ 30-40 ans versus 70 ans pour la population générale) (ANSES, 2017; Naumann et al., 2009).

1.2.2.1. Substances irritantes

Pour les substances irritantes, les POD les plus souvent utilisés sont : la concentration sans effet (nocif) observé ou NO(A)EC, la concentration minimale avec effet (nocif) observé ou LO(A)EC ou la concentration atmosphérique de la substance d'intérêt capable d'induire une réduction de 50% du taux respiratoire d'un rongeur (RD_{50}; du test d'Alarie) (Alarie, Nielsen, Andonianhaftvan et Abraham, 1995; Alarie, Schaper, Nielsen et Abraham, 1998; Brüning et al., 2014; Kupczewska-Dobecka, Soćko et Czerczak, 2006; Kuwabara et al., 2007; Nielsen et al., 2007; Schaper, 1993). Il a d'ailleurs été rapporté que bon nombre des TLV® de l'ACGIH® (qui est la base de beaucoup de VLEP internationales) est basé, du moins en partie, sur la RD_{50} (Kuwabara et al., 2007). C'est l'exemple de l'acide peracétique (Pechacek et al., 2015).

1.2.2.2. Substances à effets systémiques

Pour les substances non génotoxiques induisant des effets par voie systémique, la NO(A)EL et la LOA(E)L ont longtemps été utilisées par défaut comme POD, notamment ceux dérivés d'études chez les animal (ACGIH, 2016; EC, 2013; ECETOC, 2006; Nielsen et Øvrebø, 2008; Paustenbach et al., 2011). Néanmoins, la science de l'analyse du risque évoluant, la modélisation basée sur le concept de dose repère (BMD/C - *Benchmark Dose (ou Concentration)* » est de plus en plus recommandée et utilisée, lorsque les données le permettent (Frangos et al., 2016; Maier et al., 2010; Poet et al., 2010). L'avantage de cette stratégie d'analyse est qu'elle permet de caractériser la relation dose/réponse en considérant toutes les données pertinentes de littérature sur l'effet critique retenu, au lieu d'une seule étude clé, comme c'est le cas pour les approches NO(A)EL /LOA(E)L. Ainsi, l'analyse BMD/C permet de prédire un niveau de dose (ou de concentration) à partir d'une réponse (ou d'un effet) prédéterminé (e) (p. ex. 1, 5 ou 10% de réponse dans la population d'intérêt).

1.3. Établissement de VLEP pour substances avec données de toxicité inadéquates ou indisponibles

Par données de toxicité inadéquates, on sous-entend des données limitées ou même très limitées. Cela dit, comme nous l'avons indiqué plus haut, l'approche conventionnelle d'analyse quantitative du risque utilisée pour établir les VLEP requiert des POD qui résultent de l'analyse

des données de toxicité. Étant donné qu'une kyrielle de substances présentes dans les lieux de travail ne possèdent pas de VLEP, plusieurs approches quantitatives ont été et sont encore proposées pour établir des VLEP provisoires (ECETOC, 2006). De façon générale, l'approche conceptuelle basée sur la « relation quantitative structure-activité » (QSAR – *Quantitative Structure-Activity Relationship*) a été très largement explorée, et ce, principalement pour les substances irritantes. Soulignons que l'approche QSAR regroupe les approches basées sur la « relation quantitative structure-propriété » ou QSPR et la « relation quantitative propriété-propriété » ou QPPR.

1.3.1. Substances irritantes

Pour les substances irritantes avec données de toxicité très limitées ou inexistantes, l'évidence scientifique suggère que leurs VLEP peuvent être prédites en utilisant les données sur leurs caractéristiques structurelles et/ou propriétés physico-chimiques. Ainsi, les données de littérature indiquent que l'approche conceptuelle du QSAR a été très largement explorée pour prédire les VLEP et ce, selon deux stratégies principales : i) l'estimation directe de VLEP en utilisant comme variables prédictives des descripteurs moléculaires ou des propriétés physico-chimiques des substances d'intérêt (Debia et Krishnan, 2010; Leung et Paustenbach, 1988) et ii) la prédiction indirecte de VLEP précédée de celle d'intermédiaires. Ces derniers étaient pour la plupart des indicateurs d'irritations sensorielles, dont plus spécifiquement la RD_{50} (Abraham, Gola, Cometto-Muñiz et Cain, 2001; Abraham et al., 1990; Alarie et al., 1995; Alarie et al., 1998; ECETOC, 2006; Gagnaire, Marignac, Hecht et Héry, 2002; Hau, Connell et Richardson, 2000; Jakubowski et Czerczak, 2010; Kuwabara et al., 2007; Luan et al., 2006; Nielsen et al., 2007; Schaper, 1993). De plus, ces indicateurs étaient très souvent eux-mêmes prédits en utilisant les données sur la structure moléculaire des substances. Il a d'ailleurs été démontré que la lipophilicité des substances (c.-à-d. les coefficients de partage huile:air et *n*-octanol:eau) prédisaient la RD_{50} (Alarie et al., 1995; Alarie et al., 1998; ECETOC, 2006; Luan et al., 2006).

1.3.2. Substances à effets systémiques

Pour les substances à effets systémiques sans VLEP et n'étant ni cancérigènes, ni mutagènes, ni reprotoxiques, peu d'études ont été réalisées pour développer des solutions de rechange à l'approche par défaut pour établir des VLEP, comparativement aux substances

irritantes. Parmi les approches quantitatives proposées, énumérons : i) les « lectures croisées » ou *read-across* (ECETOC, 2006; Gordon et al., 2014), ii) l'utilisation de critères de toxicité (p. ex. NO(A)EL, LO(A)EL), iii) l'approche du parallélogramme (qui intègrent QSAR et données *in vitro* de la relation D/R) (Maier, 2011) et iv) le QSAR (Debia et Krishnan, 2010; ECETOC, 2004; El-Harbawi et Trang, 2016). Cette dernière approche a cependant été celle ayant été la plus appliquée. Ainsi, les données de littérature indiquent que les VLEP de ces substances peuvent être prédites en utilisant des critères de toxicité (c.-à-d. NO(A)EL, LO(A)EL, dose létale 50 (LD_{50}), concentration létale 50 (LC_{50})) existants ou prédits par QSAR (ECETOC, 2006; Gordon et al., 2014; Whaley et al., 2000). Il est toutefois important de souligner que ces approches nécessitent aussi l'utilisation de facteurs d'incertitude importants et restent donc dépendantes de la disponibilité des données de toxicité (c.-à-d. NO(A)EL, LO(A)EL p. ex.); ces dernières étant généralement inexistantes pour bon nombre de substances peu étudiées et sans VLEP.

Par ailleurs, l'approche basée sur le concept du seuil de préoccupation toxicologique (TTC – *Threshold of Toxicological Concern*) a aussi été suggérée pour prédire des valeurs limites provisoires pour l'analyse du risque sanitaire en milieu professionnel (ECETOC, 2006; EFSA, 2012; Hoersch, Hoffmann-Doerr et Keller, 2018). L'approche basée sur le TTC a une longue histoire d'application dans les domaines de sécurité des aliments, pharmaceutiques et cosmétiques (EFSA, 2012; EFSA et WHO, 2016; Hartung, 2017; Nielsen et Larsen, 2011; SCCS, SCHER et SCENIHR, 2012). Son efficacité pour les évaluations préliminaires des risques sanitaires qui seraient potentiellement associés aux substances peu étudiées et à données de toxicité inadéquates est de plus en plus soulignée; de même que la priorisation de celles-ci (EFSA, 2012; EFSA et WHO, 2016; Nielsen et Larsen, 2011). Du fait de sa nature probabiliste et catégorielle, l'approche se base sur l'établissement d'un seuil d'exposition pour une substance en deçà duquel le risque sanitaire serait négligeable (EFSA, 2012; EFSA et WHO, 2016; Nielsen et Larsen, 2011). Son application exige l'utilisation de FI, des données d'exposition et sur le potentiel toxique des substances. Ce dernier facteur, basé sur les similarités structurelles des substances d'intérêt avec celles de toxicité connue, permet de catégoriser les substances selon les règles de Cramer, Ford et Hall (1978) comme suit : classe I (toxicité faible - priorité faible), classe II (toxicité intermédiaire), classe III (toxicité importante - priorité élevée) et substances cancérigènes. Jusqu'ici, l'approche n'a majoritairement été utilisée ou explorée que pour évaluer

l'exposition de la population générale aux substances sans données de toxicité. L'approche pourrait cependant très bien être appliquée à l'exposition professionnelle et à notre connaissance, seule une étude l'a explorée pour pareil scénario d'exposition (Hoersch et al., 2018). Par ailleurs, le débat actuel dans la littérature scientifique relatif à cette approche porte sur l'utilisation de la dose interne d'exposition pour prédire des seuils de préoccupation toxicologique. Cela demeure un axe de recherche encore très peu exploré pour l'heure.

Chapitre 2. Contexte de la thèse

2.1. Problématique

Plusieurs substances chimiques organiques existantes (largement utilisées dans l'industrie et le commerce), nouvelles (sous-produits de procédés) ou émergentes qui pourraient se retrouver dans l'air ambiant des lieux de travail ne possèdent pas de VLEP (Brandys et Brandys, 2008; Mulhausen et al., 2006; Paustenbach et al., 2011; Scheffers et al., 2016; Schenk, Hansson, Ruden et Gilek, 2008). Par ailleurs, cette situation risque peu de s'améliorer. En effet, du fait entre autres des nouvelles technologies, le nombre de substances en circulation (p. ex. produits commercialisés, déchets et sous-produits de procédés et fabrication) ne cesse de croître, occasionnant entre autres l'apparition de nouvelles entités aux structures chimiques parfois (très) complexes et aux propriétés physico-chimiques particulières, comme c'est l'exemple de nanomatériaux (Borak et Brosseau, 2015; Gordon et al., 2014). De plus, avec l'amélioration incessante des méthodes analytiques (et technologiques), de plus en plus de substances organiques (p. ex. impuretés, métabolites,) jadis non détectées dans l'air ambiant du milieu professionnel, le sont maintenant, et souvent à de très faibles concentrations (EFSA, 2012; Gordon et al., 2014). Nous constatons donc actuellement un déséquilibre entre les ressources disponibles pour développer des VLEP et le nombre de substances nécessitant une telle évaluation (Whaley et al., 2000). Cette situation est particulièrement difficile pour les petites et moyennes entreprises qui, comme nous l'avons mentionné en introduction générale et au chapitre 1, sont très souvent désavantagées du fait de leurs ressources (financières et humaines notamment) limitées pour développer des VLEP internes ou du moins des stratégies de contrôle de l'exposition (Howard, 2005).

Plusieurs raisons sont évoquées dans la littérature pour expliquer le manque de VLEP pour un nombre impressionnant de substances dont spécifiquement le manque de données de toxicité adéquates (Borak et Brosseau, 2015; Debia et Krishnan, 2010; Ding, Schenk, Malkiewicz et Hansson, 2011; Drew et Frangos, 2007; Gordon et al., 2014). Il serait cependant impossible des points de vue pratique, économique et éthique, de réaliser des tests de toxicité pour chacune des substances en circulation et chez toutes les espèces pertinentes (ECETOC, 2006; Gordon et al., 2014; Mulhausen et al., 2006; Paustenbach et al., 2011; Vaughan et Rajan-Sithamparanadarajah, 2017; Whaley et al., 2000). Par ailleurs, le nouveau paradigme de la toxicologie valorise et recommande de plus en plus les solutions de rechange aux tests de

toxicité traditionnels (Adler et al., 2011; Bessems et al., 2014; NRC, 2007). C'est l'exemple des programmes ToxCast et Tox21 de l'agence américaine de protection de l'environnement (U.S. EPA – *Environmental Protection Agency*).

Ainsi, au cours des dernières décennies, un changement de paradigme s'est initié au sein de la communauté scientifique, prônant le remplacement des approches quantitatives classiques par des approches qualitatives d'analyse et gestion du risque sanitaire professionnel (ECETOC, 2006; Howard, 2005). Parmi les approches qualitatives proposées, énumérons celles basées sur les « *kick-off levels* » (DOHSBASE, 2014) et celles s'appuyant sur le concept de « bandes de dangerosité » (*hazard banding*). En ce qui concerne ces dernières, il s'agit notamment des approches de l'OEB (Guest, 1998), de « gestion graduée des risques » (*control banding)* (Scheffers et al., 2016; Vaughan et Rajan-Sithamparanadarajah, 2017; Zalk et Nelson, 2008) et celle de la priorisation du risque (*Risk Prioritization*) (ECETOC, 2004; Marquart et al., 2008). Or, ces approches qualitatives sont généralement axées sur la prescription de stratégies de contrôle de risque (p. ex. ventilation, contrôle de l'ingénierie, confinement). Notons cependant qu'un recours trop fréquent à ces approches au détriment d'approches quantitatives (basées sur des données) pourrait à long terme remettre tout le système en question du fait par exemple du manque de données de toxicité nécessaires pour les valider (Borak et Brosseau, 2015). Ceci, ajouté à l'utilité des VLEP mentionnée au chapitre 1, renforce la légitimité et la pertinence des approches quantitatives pour développer et établir des VLEP, même pour des substances ayant très peu ou pas de données de toxicité.

Ainsi, plusieurs initiatives ont été mises de l'avant au cours des dernières décennies pour explorer ou développer de nouvelles stratégies et approches quantitatives de développement et d'établissement de VLEP. La revue des données publiées indique cependant que contrairement aux substances irritantes, peu de recherches ont été effectuées pour le développement de VLEP pour des substances à effets systémiques (voir chapitre 1). De plus, la majorité des approches proposées était basée sur des indicateurs de dose externe d'exposition (p. ex. NO(A)EL). La dose interne est pourtant reconnue comme étant un meilleur indicateur de toxicité. Par ailleurs, l'évidence scientifique supportant l'association entre l'exposition aux substances chimiques organiques, notamment les composés organiques volatils (p. ex. vapeurs de solvants, peintures, colles, produits de nettoyage), et certaines maladies professionnelles (p. ex. irritations des yeux

et des voies respiratoires supérieures, effets neurologiques et respiratoires, cancers) n'est plus à démontrer (ACGIH, 2016; Austin, 2004; Kuwabara et al., 2007; Luan et al., 2006). La situation actuelle invite donc sérieusement à réviser les processus d'analyse et de gestion des risques sanitaires en SST, et à prioriser le développement de solutions de rechange pour la dérivation quantitative des valeurs limites pour l'exposition professionnelle.

2.2. Hypothèse de recherche

Une approche qui intègre l'information sur la structure moléculaire, les paramètres physiologiques de l'espèce et les modélisations de type « relation quantitative structure (ou propriété) -propriété » (QPPR (ou QSPR)) et pharmacocinétique à base physiologique (PBPK) permettrait de prédire des valeurs de seuils de préoccupation toxicologique pour permettre la caractérisation des risques sanitaires associés aux substances organiques sans VLEP.

2.3. Objectifs

La présente thèse a pour objectif de développer des seuils de préoccupation toxicologique pour permettre la caractérisation des risques sanitaires associés aux substances organiques sans VLEP en utilisant la structure moléculaire et la dose interne. Pour ce faire, trois sous-objectifs ont été identifiés, à savoir :

1- Prédire des seuils de préoccupation toxicologique pour l'exposition professionnelle aux substances chimiques organiques à effets systémiques;

2- Développer des modèles intégrés de type QPPR-PBPK prédictifs de la toxicocinétique et des doses internes des substances chimiques organiques;

3- À partir des doses internes et de la structure moléculaire, prédire des seuils de préoccupation toxicologique et développer des modèles prédictifs de valeurs limites, pour l'exposition professionnelle aux substances chimiques organiques.

Chapitre 3. Derivation of Occupational Thresholds of Toxicological Concern for Systemically Acting Noncarcinogenic Organic Chemicals

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Derivation of Occupational Thresholds of Toxicological Concern for Systemically Acting Noncarcinogenic Organic Chemicals

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Abstract

Many substances in workplace do not have occupational exposure limits. The threshold of toxicological concern (TTC) principle is part of the hierarchy of approaches useful in occupational health risk assessment. The aim of this study was to derive occupational TTCs (OTTCs) reflecting the airborne concentrations below which no significant risk to workers would be anticipated. A reference dataset consisting of the 8-h threshold limit values -Time-Weighted Average for 280 organic substances was compiled. Each substance was classified into low (class I), intermediate (class II), or high (class III) hazard categories *as per* Cramer rules. For each chemical, *n*-octanol:water partition coefficient and vapor pressure along with the molecular weight were used to predict the blood:air partition coefficient. The blood:air partition coefficient along with data on water solubility and ventilation rate allowed the prediction of pulmonary retention factor and absorbed dose in workers. For each Cramer class, the distribution of the predicted doses was analyzed to identify the various percentile values corresponding to the OTTC. Accordingly, for Cramer classes I-III, the OTTCs derived in this study correspond to 0.15, 0.0085, and 0.006 mmol/d, respectively, at the 10^{th} percentile level, while these values were 1.5, 0.09 and 0.03 mmol/d at the 25^{th} percentile level. The proposed OTTCs are not meant to replace the traditional occupational exposure limits, but can be used in data-poor situations along with exposure estimates to support screening level risk assessment and prioritization.

Key words: threshold of toxicological concern (TTC); occupational exposure limit (OEL); occupational TTC (OTTC); quantitative property-property relationships (QPPR); pulmonary retention factor; occupational health risk assessment.

3.1. Introduction

Workers in many industrial settings are exposed to a large number of existing, new or emerging organic substances that might impact their health. In this regard, atmospheric occupational exposure limits (OELs) are useful for the assessment of, and protection from, the potential health effects that may result from overexposure to airborne chemicals (ACGIH, 2016; ECETOC, 2006). The OELs, specifically the threshold limit values (TLVs) refer to airborne concentrations of chemical substances and represent conditions under which it is believed that *nearly all* workers may be repeatedly exposed, day after day, over a working lifetime, without adverse health effects (http://www.acgih.org/tlv-bei-guidelines/tlv-chemical-substances-introduction). Many organic chemicals in the workplace do not have OELs and this has long been attributed to the lack of toxicity data (ECETOC, 2006; Gordon *et al.*, 2014). For instance, out of the several thousand organic substances that may be found in occupational settings, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended TLVs for only a small percentage of the universe of workplace contaminants as of 2016. When OEL for a chemical is not available or has not been developed, Deveau *et al.* (2015) described the usefulness of a number of alternative methods comprising a hierarchy, in which the lower level approaches would be associated with greater uncertainty and less resources keeping in perspective the purpose of the occupational risk assessment.

Typically, chemicals can be viewed as belonging to one of the 2 following categories depending on the availability of data required to confidently develop an OEL: data-poor and data-rich. In this latter case, well-established risk assessment methods exist for setting OELs; and they usually rely upon an integrated analysis of the critical health effects, dose-response relationship, and extrapolation methods (EC, 2013; Nielsen and Øvrebø, 2008; Paustenbach *et al.*, 2011; Vincent, 1998). However, this is not the case for data-poor chemical substances (ie, for which there is no or limited toxicity data). Even though many past efforts have focused to develop quantitative animal-replacement approaches for OEL setting of irritants (Abraham *et al.*, 1990; Alarie *et al.*, 1998; Debia and Krishnan, 2010; ECETOC, 2006; Gagnaire *et al.*, 2002; Jakubowski and Czerczak, 2010; Kuwabara *et al.*, 2007; Leung and Paustenbach, 1988; Luan *et al.*, 2006; Nielsen *et al.*, 2007; Schaper, 1993), this is not the case with systemically acting noncarcinogenic workplace contaminants. For such chemicals, the following alternative

methods have been applied in a limited manner for developing OELs: (1) read-across, (2) use of acute toxicity criteria and (3) quantitative structure-activity relationships (QSARs) (Debia and Krishnan, 2010; ECETOC, 2006; El-Harbawi and Trang, 2016). Moreover, the occupational exposure banding (OEB) and the threshold of toxicological concern (TTC), representing qualitative to semiquantitative approaches, have also been proposed for providing screening values to support risk assessment and management (Deveau *et al.*, 2015; ECETOC, 2006; Kroes *et al.*, 2004; NIOSH, 2017).

Although OEB (also referred to as hazard banding) assigns chemicals to specific categories based on their potency and adverse health effects, the TTC approach relies upon the chemical structure of data-poor substances to assign an exposure level or dose below which no significant risk to workers would be anticipated based on thresholds derived from distributions of potency drawn from a relevant toxicity database (Deveau *et al.*, 2015; Felter *et al.*, 2009; Kroes *et al.*, 2000, 2004). The TTC concept was first applied by Munro et al. (1996, 1999) for the safety evaluation of flavoring substances. Based on the analysis of chronic toxicity data on 137, 28 and 448 nongenotoxic substances belonging to Cramer *et al.* (1978) structural classes I, II and III, respectively, Munro *et al.* (1996) derived human exposure TTC values of 30, 9, and 1.5 μg/kg body weight/day for oral exposure. These oral TTCs have been evaluated for use by several regulatory agencies (EFSA, 2012; Nielsen and Larsen, 2011; SCCS *et al.*, 2012). Also, they are integrated into the Kroes *et al.* (2004) decision tree and its extensions to facilitate a structured application of the approach. The TTC-based approach, well supported thus far for chronic exposure, has extensively been applied in the food and pharmaceutical industries to support risk assessment for general population exposed by ingestion (Kroes and Kozianowski, 2002; Mons *et al.*, 2013; Munro *et al.*, 1999); further efforts have focused on the dermal route (Kroes *et al.*, 2007; Worth *et al.*, 2012), and inhalation route of exposure (Carthew *et al.*, 2009; Drew and Frangos, 2007; Escher *et al.*, 2010; Grant *et al.*, 2007; Hennes, 2012; Schüürmann *et al.*, 2016; Tluczkiewicz *et al.*, 2016). The application of TTC principle to the airborne chemicals thus far has not been based on human data or human exposure guidance values. In this regard, its application to occupational health risk assessment could involve an examination of the distribution of OELs that have been generated over several decades to be protective of worker health. But this has never been attempted as of yet. Therefore, the aim of this study was to derive occupational TTCs (OTTCs) based on distributional analysis of OELs in view of potentially

identifying the exposure level or dose below which no significant risk to workers would be anticipated.

3.2. Materials and Methods

For this study, a reference dataset of OEL values for 280 systemically acting organic chemicals was constructed. Then, their chemical structure information was used to assign the Cramer class ("OEL dataset and Cramer classification" Section), and estimate their daily dose in workers associated with the occupational exposure at the OEL level ("PRF and estimation of workers' daily dose" Section). Subsequently, as described in "Derivation of the OTTC values" Section, statistical analyses of the estimated daily doses were undertaken to identify the TTCs corresponding to 8-h occupational exposure (ie, OTTCs), and these threshold values were then converted to airborne concentrations for each of the 3 Cramer classes.

3.2.1. OEL dataset and Cramer classification

Figure 1 is a flowchart illustrating the steps that were followed for compiling a set of substances for this study. The TLVs of the American Conference of Governmental Industrial Hygienists (ACGIH) were chosen as the only source of OELs for the current analyses because they are known to be extensive and evolving, with a history of application around the world. ACGIH TLVs are health-based values, which are given with the indication of target organs such that we could readily identify those that are based on systemic effects. Furthermore, these TLVs represent a scientific opinion formulated following a review of existing peer-reviewed scientific literature in industrial hygiene, toxicology, occupational medicine, and epidemiology, regarding the level of exposure that the typical worker can experience without adverse health effects (http://www.acgih.org/tlv-bei-guidelines/tlv-chemical-substances-introduction). Of the 3 categories of values published by ACGIH, (1) 8-h TLV-Time-Weighted Average (8-h TLV-TWA), (2) TLV-Short-Term Exposure Limit, and (3) TLV-Ceiling, the 8-h TLV-TWAs were selected as the most suitable for application of the Cramer classification to systemically acting organic chemicals (EFSA, 2012; EFSA and WHO, 2016; Tluczkiewicz *et al.*, 2016). As such,

only the TLV listed in the table from the 'Adopted Values' section of the TLV booklet published by the ACGIH in 2016 were sourced. The values in the "2016 Notice of intended changes" list (below the adopted values list) were not accounted for. Since the tables in the booklet lists both the TLV values and the adverse health effects used for their derivation, the identification of the type of adverse health effects (eg, systemic effects, irritation, sensitization) was performed by referring to the TLV basis column of the table. The 8-h TLV-TWAs were noted with their original units, ie, either part per million (ppm) or mg/m^3. Also, the Chemical Abstract Service Register Number (CASRN) was used as the preferred form for substances identification and those with CASRN not referring to a single substance or not recognized by the programs used for this work were not accounted for. Thus, out of the 508 chemicals with values of 8-h TLV-TWA, 139 chemicals were excluded from this analysis as their TLVs were solely based on irritation, sensitization, or dental erosion (ie, sucrose). Afterwards, the Kroes *et al.* (2004)'s decision tree, as revised by EFSA (2012) and EFSA and WHO (2016) was applied to the selected systemically acting noncarcinogenic organic chemicals for further analyses (Figure 1).

Each organic substance identified in the section above was assigned to a Cramer structural class (I-III) using the software program Toxtree, version 2.6.13, which incorporates the original Cramer *et al.* (1978)'s decision tree and its extensions (EFSA and WHO, 2016; Tluczkiewicz *et al.*, 2011). Similar to previous work on food contaminants (Cramer *et al.*, 1978; Kroes *et al.*, 2004; Munro *et al.*, 1996), this work would indicate that Cramer class I consists of occupational contaminants of low order of toxicity, possessing simple structures and amenable to efficient metabolism to innocuous products; class II contains occupational contaminants that are less innocuous than those belonging to class I but without indication of potential toxicity that characterizes class III substances; and class III occupational contaminants represent those that are metabolized to potentially toxic reactive products and contain structural features that do not support presumption of innocuity or absence of risk to worker health. The result of the above classification of 280 systemically acting organic chemicals was compiled in Microsoft Excel, and it specifically included the chemical name, CASRN, OEL (ie, 8-h TLV-TWA) and Cramer class. Additionally, the following physicochemical properties were also included: molecular weight (MW), *n*-octanol:water partition coefficient ($LogP_{ow}$), vapor pressure (VP), and water solubility, and these were input parameters for computing the pulmonary retention factor (PRF) and absorbed dose in workers ("PRF and estimation of workers' daily dose" Section).

3.2.2. PRF and estimation of workers' daily dose

The TLVs refer to the atmospheric concentrations of chemical substances (ACGIH, 2016). However, for systemically-acting inhaled compounds, the amount absorbed into systemic circulation is more relevant for toxicity assessment. As such, for each chemical in the reference dataset, a daily dose reflective of the fraction of the TLV-TWA absorbed by a worker while performing a light activity during a conventional 8-h workday (ie, the daily dose of a worker) was computed as follows (Jakubowski and Czerczak, 2009):

$$\mathrm{AD} = \frac{\mathrm{TLV}\times\mathrm{T}\times\mathrm{V}\times\mathrm{PRF}}{\mathrm{MW}} \qquad (1)$$

where AD (mmol/d), absorbed dose; TLV (mg/m^3), concentration in the air corresponding to the 8-h TLV-TWA; T (h), duration of exposure (according to the 8-h TLV-TWA's definition, a conventional 8-h workday was used); V (m^3/h), lung ventilation rate (10 m^3/8 h/d for a light activity); PRF, ie, the fraction of the dose absorbed by the inhalation route; MW (g/mol), molecular weight.

Although the ppm unit is suited for the comparison of chemicals on a molar basis, the mg/m^3 unit allows the calculation of dose on a body weight basis (Escher *et al.*, 2010). Since the chemicals in the reference dataset are mostly gases or vapors, the 8-h TLV-TWA values in ppm were converted to the corresponding mg/m^3 unit as follows:

$$\mathrm{TLV\ (mg/m^3)} = \frac{\mathrm{TLV\ (ppm)} \times \mathrm{MW(g/mol)}}{24.45\ \mathrm{(l/mol)}} \qquad (2)$$

where 24.45, the molar volume of air in liters at the Standard Temperature and Pressure (25ºC and 760 torr) (ACGIH, 2016).

The PRF, used conventionally in the inhaled dose calculations as shown in equation (1), is generally assigned a default value of 100%. However, the absorption of inhaled

chemicals highly depends on substance features such as blood:air partition coefficient, lipophilicity and water solubility among other factors (Jakubowski and Czerczak, 2009; Kuempel *et al.*, 2015). As such, the blood to air partition coefficients (P_{ba}) were used to predict the PRF as per Jakubowski and Czerczak (2009) in a 2-tier approach in which cut-off values were determined by water solubility, as follows:

- For substances with water solubility higher than 10 mg/l (w+),

$$PRF_{w+} = (36.608 + 9.799 \times LogP_{ba})/100 \quad (3)$$

- For substances exhibiting water solubility < 10 mg/l (w-),

$$PRF_{w-} = (26.810 + 21.022 \times LogP_{ba})/100 \quad (4)$$

Since the PRF can only take values between 0 and 1, all the chemicals from our dataset with predicted values of PRF higher or equal to 1 were assigned a PRF of 1 and those with a predicted value less or equal to the minimum of all the predicted values of PRF were assigned the minimum predicted value of 0.07.

The only input parameter required for predicting PRF according to the QSAR approach of Jakubowski and Czerczak (2009) is P_{ba}, for which several quantitative structure-property and property-property relationships (QPPRs) are available. For the purpose of this study, the following QPPR model of Buist *et al.* (2012) was chosen due to its applicability to humans, simplicity, relevant application domain and easily obtainable input parameters:

$$LogP_{ba} = 6.96 - 1.04 \times Log(VP) - 0.533 \times LogP_{ow} - 0.00495 \times MW \quad (5)$$

where, P_{ba} (unitless), blood:air partition coefficient; VP (Pa at 25°C), vapor pressure; P_{ow}

(unitless), *n*-octanol:water partition coefficient; MW (g/mol), molecular weight.

The data on the MW (g/mol), VP (Pa at 25^{o}C), LogP_{ow} (unitless) and the water solubility (WS; g/L) were obtained using U.S. EPA's EPI Suite, version 4.11. Since all the chemicals selected for analyses did not have experimental data on PRF and P_{ba}, a subset of 27 substances with data for both of these parameters was compiled for comparison with the predictions obtained as per Jakubowski and Czerczak (2009) and Buist *et al*. (2012). In effect, for the PRF, the means of the experimental values reported in Jakubowski and Czerczak (2009) were computed. However, the experimental data on P_{ba} were obtained from the compilation of Buist *et al.* (2012), with the missing values from Jakubowski and Czerczak (2009).

3.2.3. Derivation of the OTTC values

The OTTC values were derived similar to the approach initially proposed by Munro *et al.* (1996) for oral exposure. In their analyses, Munro and coworkers applied a 100-fold composite uncertainty factor to the fifth percentile of NOEL (subsequently referred to as NOAEL) for each structural class to translate this value into a human exposure threshold. In a similar manner, for each Cramer class, the cumulative distribution of the workers' daily doses (based on 8-h TLV-TWA) was constructed. However, contrary to Munro et al.'s use of a composite uncertainty factor (for intra- and interspecies extrapolations) for translating the rodent data-derived fifth percentiles into human exposure levels, such a factor was not used in this study since it was already accounted for while establishing the 8-h TLV-TWA for occupational exposure. Hence, the calculated percentiles were directly used as the basis for deriving estimates that would serve as thresholds of occupational exposure to chemicals belonging to each Cramer class, ie, the OTTCs. It should be noted that the calculations and comparisons of the worker daily doses associated with 8h TLV-TWA were performed on a molar basis (mmol/d) in this study, contrary to all previous studies on TTC derivation that

based their analyses of potency across the chemicals and classes on a milligram basis. Then, to allow comparison with the TTC values from other studies, the OTTCs were further converted in μg/person/day unit by means of eq. (6). Furthermore, the OTTCs (mmol/d) were then translated into air concentrations for workers using eq (7). All interconversions of OTTCs derived in this study were performed using a breathing rate for a work day of 10 m^3 along with the corresponding MW of each chemical in the reference dataset.

$$\mathrm{OTTC(mg/person/d)} = \mathrm{OTTC(mmol/person/day)} \times \mathrm{MW\ (mg/mmol)} \quad (6)$$

$$\mathrm{OTTC\ (mg/m^3)} = \frac{\mathrm{OTTC\ (mg/person/d)}}{\mathrm{V(m^3/d)}} \quad (7)$$

3.2.4. Data and statistical analysis

The descriptive statistics were obtained for the dataset on 8-h TLV-TWAs and the worker daily doses. For the latter, the distributions and the corresponding parametric percentiles in the 3 structural classes were obtained. For that, the data were first graphically represented with boxplot. To assess the impact of the hazard class on the toxicity, the distributions of the workers' daily doses for each Cramer class were evaluated with several hypothesis tests. Thus, the normality of the workers' daily dose data from each structural class was initially verified by performing the Jarque-Bera test with a *p* value of .05 as the significance level. Since the normality tests were negative for both the distributions of daily doses and that of their logarithms, the distributions of the doses were then treated non-parametrically. As such, some distribution fittings were performed in order to assess which distribution fits better the data. This exercise resulted in the lognormal distribution being chosen over the Weibull and programmatically fitted to the workers' daily dose data. The resulting fits were evaluated with chi-square goodness-of-fit test and confirmed with the one-

sample Kolmogorov-Smirnov test. The fitted distributions were evaluated by the Kruskal-Wallis test. They were also compared with each other by means of the multiple comparison test (type of analysis of variance [ANOVA]). All computations and statistical analyses of the data were performed using MATLAB and its Statistics and Machine Learning Toolbox, both version R2016b.

3.3. Results

3.3.1. OEL Dataset and Cramer Classification

The application of the revised decision tree of Kroes *et al.* (2004) led to the removal of 89 substances that belonged to the exclusionary categories of the approach. Chemical figures among them are: 16 high potency carcinogens (genotoxics, aflatoxin-like, azoxy- or N-nitroso compounds and benzidines), 43 organophosphates and carbamates, 2 polyhalogenated dioxins/dibenzo furans and dioxin-like polyhalogenated biphenyls, 10 organometallics, 1 organosilicon compound, 3 allergens, 10 mixtures and 4 nonstructurally defined substances (Figure 1). Further, from the category of carcinogens, the following 12 compounds with notations A1 ("confirmed human carcinogen") or A2 ("suspected human carcinogen") in the TLV booklet were excluded: 1,2,3-trichloropropane (CASRN 96-18-4); 1,3-butadiene (CASRN 106-99-0); 4,4'-methylene bis(2-chloroaniline) (CASRN 101-14-4); benzene (CASRN 71-43-2); bis-(chloromethyl)ether (CASRN 542-88-1); dimethyl carbamoyl chloride (CASRN 79-44-7); ethylene oxide (CASRN 75-21-8); vinyl bromide (CASRN 593-60-2); vinyl chloride (CASRN 75-01-4); vinyl fluoride (CASRN 75-02-5); carbon tetrachloride (CASRN 56-23-5) and trichloroethylene (CASRN 79-01-6).

Overall, a reference dataset of 280 systemically acting and noncarcinogenic organic chemicals with 8-h TLV-TWA as well as data on physicochemical properties was compiled (see Supplementary Material). The chemicals represent a wide variety of molecular structures and toxicological endpoints (eg, liver toxicity, kidney toxicity, cardiovascular toxicity, pulmonary toxicity, neurotoxicity, reproductive toxicity and developmental toxicity). The 8-h TLV-TWAs ranged from 0.002 to 9000 mg/m^3 (mean ± SD; 353 ± 1032). Table 1 shows the descriptive

statistics of the 8-h TLV-TWAs for the entire dataset and per Cramer class. The physicochemical properties domain of the dataset was broad: MW ranged from 28.01 to 431.10 g/mol (mean ± SD; 147 ± 89); log n-octanol:water partition coefficient from -2.82 to 8.55 (mean ± SD, 1.92± 1.84); log VP (Pa) from -9.05 to 6.62 (mean ± SD, 1.76 ± 3.20) and water solubility ranged from negligible to 1000 g/l (mean ± SD, 114.54 ± 275.23).

The Cramer classification of the chemicals in the OEL dataset constructed for this study resulted in assigning of 30% to class I, 4% to class II and 66% to class III. Similar allocation was previously reported for TTC derivation for the oral route (Munro *et al.*, 1996) and inhalation route (Escher *et al.*, 2010) for the general population.

3.3.2. PRF and Estimation of Workers' Daily Dose

For 23 out of 27 chemicals, the predicted human P_{ba} values, on average, varied from the experimental values by a factor of 1.2 (range: 0.1 – 3.1). However, the QSAR predictions of P_{ba} differed from the corresponding experimental values by factors of 10.5 for acrylonitrile, 20.4 for dimethylformamide, 69.2 for ethylene glycol monoethyl ether acetate, and 10.2 for nitrobenzene (Table 2). Using these values of P_{ba}, the predictions of PRF were obtained, which on average were within a factor of 1.1 (SD, 0.2, n = 27) of the reported experimental values (Table 2). Due to the reasonable agreement between the predicted and empirical values of PRF for the subset of 27 chemicals, this parameter was then predicted for all the chemicals of the entire dataset to calculate the daily dose to the worker.

The predicted worker daily doses ranged from 2.7×10^{-5} to 682.51 mmol/person/day for the entire dataset. For class I chemicals, these values ranged from 4.3×10^{-5} to 682.51 mmol/d; for class II chemicals, from 2.7×10^{-5} to 25.42 mmol/d; and for class III chemicals, from 7.02×10^{-5} to 134.63 mmol/d. Table 1 shows the descriptive statistics of the predicted daily doses for the entire dataset and per Cramer class.

As seen on the boxplot from Figure 2 and other visual checks, the value of 682.51 mmol/person/day (for carbon dioxide) from class I stood apart as an outlier and was therefore excluded for subsequent analyses. The boxplot also shows that (1) the doses for class I chemicals are higher than those from class III, (2) there is less variability among the calculated doses for class I chemicals as compared to class III, and (3) class II exhibits the highest variability. It appears that the medians of classes I and III are different, which is not the case for class II when

compared with the other classes. The results from the Jarque-Bera test indicated that the distributions of the daily doses were not normal (p = .001 for classes I and III; p = .107 for class II). This normality test also indicated that the logarithm of the daily dose values from class I were not normally distributed. Even though the results for the logarithm of the daily dose values from classes II and III seemed to indicate normality, they were not significant (p = .221). The chi-square goodness-of-fit test indicated that the daily doses were lognormally distributed at the 1% significance level (p = .013) and this was confirmed by the one-sample Kolmogorov-Smirnov test. Since the notches from classes I and III in the boxplot (Figure 2) do not overlap, it can be assumed, with 95% CI that the true medians of the daily doses in each of these classes do differ. Indeed, the Kruskal-Wallis test indicated that the distributions of the data from the classes I and III are statistically different ($p = 5.462 \times 10^{-15}$) from one another at 1% significance level (Table 3). Additionally, the pairwise comparison results indicated a significant difference between the mean ranks of classes I and III (Table 3). However, the mean ranks of these 2 classes were not significantly different from class II, as indicated by the 2-sample Kolmogorov-Smirnov test for classes II and III (p = .896; statistic = .067).

3.3.3. Derivation of the Occupational Thresholds of Toxicological Concern

Figure 3 illustrates the cumulative distribution function of the daily doses of occupational contaminants belonging to each Cramer class. Table 4 shows the 5th, 10th, and 25th calculated parametric percentiles from the empirical cumulative density function of the daily doses from each Cramer class. Since the calculated daily doses represent simple translation of the external exposure (ie, the 8-h TLV-TWA) into absorbed dose in workers, no uncertainty factor was applied in this study.

Accordingly, for Cramer classes I-III, the OTTCs derived in this study correspond to 0.07, 0.004 and 0.003 mmol/worker/day at the 5th percentile level, while the values were 0.15, 0.0085 and 0.006 mmol/worker/day at the 10th percentile level. However, the difference between classes II and III was more marked at the 25th percentile level (0.09 and 0.03 mmol/worker/day, respectively). TTC values based on combined distribution of values for classes II and III were similar to the individual class values obtained for class III (data not shown).

Table 5 presents, for the 3 Cramer classes, the range of physicochemical properties covered by the chemicals belonging to the reference dataset.

3.4. Discussion

OELs are valuable benchmarks of maximum acceptable air concentrations meant for the protection of workers from overexposure to air-borne chemicals. With ever increasing number of new materials in commerce as well as developments in analytical techniques and engineering, many chemicals and chemical mixtures still do not have TLVs. A hierarchy of tools, representing different levels of data requirement, are available for application in occupational health risk assessment (Deveau *et al.*, 2015). They range from hazard banding approaches requiring the least amount of data to the health-based OELs requiring the most extensive data on physicochemical and toxicological characteristics of the chemical. For data poor chemicals lacking OELs, control banding has proven to be a pragmatic risk management tool for hygienists and this article focused on developing OTTCs based on distributional analysis of the TLVs of systemically acting noncarcinogenic chemicals.

The OTTCs developed in this study are based on the notion that an untested chemical would exhibit an airborne concentration below which no significant risk to workers would be anticipated and the OTTCs are to be used as part of a decision tree framework integrating information on occupational uptake of chemicals (Kroes *et al.*, 2004). The OTTCs can also be used as a part of the prioritization tools used in the context of integrated testing strategy for occupational toxicants or used as a screening level assessment tool to compare with predicted air borne concentrations associated with the proposed industrial applications of an untested chemical. In this regard, this work has allowed to classify systemically acting noncarcinogenic chemicals retrieved from the TLV database based on Cramer *et al.* (1978) for the first time.

The TTC principle originally developed and implemented for food contaminants was based on NOAELs for the oral route obtained for nonvolatile organic chemicals in animals (Kroes *et al.*, 2004; Munro *et al.*, 1996, 1999). But the current study developed OTTC values on the basis of TLV values for airborne contaminants established by ACGIH. Although the TTC approach used a composite uncertainty factor of 100 to account for interspecies (animal to human) and interindividual differences, the OTTC approach draws upon the inhalation concentrations corresponding to exposure limit values set for workers (the population of interest) such that no further uncertainty factors were applied. Moreover, while traditional TTC approach does not correct the dose for oral bioavailability or fraction absorbed, this study

accounted for the fraction absorbed by the inhalation route using an empirical approach based on blood:air partition coefficients of chemicals (Jakubowski and Czerczak, 2009).

Aside the deficiency of not accounting for the route-specific absorption fraction, most of the previous studies on inhalation TTCs have been challenged with the route, species, severity and duration adjustment issues as well as dealing with the reality of data of differing quality from multiple sources or laboratories and use of different classification schemes (Carthew *et al.*, 2009; Drew, 2010; Drew and Frangos, 2007; Escher *et al.*, 2010; Grant *et al.*, 2007; Schüürmann *et al.*, 2016; Tluczkiewicz *et al.*, 2016). This study, by focusing on the use of the TLV database as the sole data source, chose to use exposure limits developed for the population of interest which have evolved over the past several decades. One recent publication reported the derivation of internal dose-based TTC to facilitate route to route extrapolation, eg, oral to inhalation extrapolation of TTCs (Partosch *et al.*, 2015). These authors, by accounting for oral bioavailability, reported TTCs of 6.9 and 0.1 µg/kg/d (based on fifth percentile values) for class I and class II/III, whilst values based on the 10^{th} percentile were 38.6 and 1.5 µg/kg/d, respectively. In this study, however, Partosch *et al.* (2015) combined the NOAELs from animal studies with predicted human bioavailability factors for developing the internal dose-based TTCs. Specifically, these authors assumed 100% oral bioavailability in animals but a lower oral bioavailability in humans as determined with a QSAR approach. The animal-human differences in metabolism or other kinetic determinants of these substances were not taken into account. Evidently, assuming 100% bioavailability of the oral NOAELs is the least health protective or the most uncertain option, because the critical point of departure representing the starting route for the extrapolation is not corrected for bioavailability or first pass effect. Therefore, the internal dose-based TTC derived by Partosch *et al.* (2015) is not directly relevant or comparable to the OTTCs for the inhalation route derived in this study.

The direct comparison of the OTTC values from this study with the TTC values of Kroes *et al.* (2004) is not straight forward either, because of 3 factors: (1) inhalation-oral route differences in absorption, (2) duration of exposure (7 d/wk, 24 h/d for general population vs 5 d/wk, 8 h/d in workers) and (3) the component of sensitive subpopulation (elderly, pregnant women, infants, etc.) covered with the use of a factor of 10 in the TTC approach in contrast to the TLVs used in this study for deriving OTTC which do not routinely comprise of such a factor. However, for the purpose of indicative comparison, NOEL values of 3, 0.9 and 0.15 mg/kg/d

for the 3 classes identified by Kroes *et al.* (2004, 2007) can be divided by the interspecies uncertainty factor of 10 to derive human-equivalent toxicity thresholds of 300, 90 and 15 μg/kg/d, respectively (or 18, 5.4 or 0.9 mg/d for the 3 classes, using a body weight of 60 kg). Dividing by a typical worker's inhalation rate of 10 m^3/d, these values would yield inhalation concentrations of 1.8, 0.54 and 0.1 mg/m^3 for workers. In this study, we derived 10th percentile values of 0.82, 0.06 and 0.04 mg/m^3 for classes I-III, based on the OEL for systemically acting noncarcinogenic chemicals from the TLV database. The values derived in this study are all lower than what would be derived from Kroes *et al.* (2004) values, while noting that the latter are not corrected for inhalation absorption fraction and oral bioavailability.

In applying the TTC principle to occupational health risk assessment, ECETOC (2006) developed examples in which the TTC for each class (equal to animal NOAEL divided by uncertainty factors of 10 × 10) was multiplied by human body weight (60 kg) and divided by a worker's daily breathing rate of 10 m^3/d. Accordingly, ECETOC (2006) initially reported a derived OTTC of 0.18 mg/m^3 for all Cramer class I substances (ie, acetone, sec-butanol, butyl acetate, cyclohexanol and toluene; 3 mg/kg/d × 60 kg/[10 m^3 × 10 × 10]). Since the resulting value of 0.18 mg/m^3 was very small compared with the recommended OELs for these substances (ranging from 191 to 1210 mg/m^3), an alternative method was described by ECETOC (2006), in which the uncertainty factor of 100 was removed. Therefore, the resulting OTTC was 100 times greater than the initial values. For example, for acrylic acid, using a TTC value for class II along with a human BW of 60 kg and breathing rate of 10 m^3, the following OEL was derived: 0.9 × 60/10 = 5.4 mg/m^3 (instead of 0.054 m/m^3 obtained with adjustment for inter- and intraspecies differences). Both approaches used by ECETOC (2006) are questionable, since no adjustment for inhaled fraction or oral bioavailability was made, and the magnitude of uncertainty factors used was either 1 or 100 (not defensible for application to worker population). The TTCs are intended for use as a lower tier approach in data-poor situations. As such, instead of comparing the OTTCs with OEL (ECETOC, 2006), the more appropriate approach would be to integrate them within a decision tree that considers the worker exposure associated with intended uses of the given chemical. When the estimated exposure level is well below the TTC for the structural class to which the chemical belongs, then there is no concern of safety or indication of a high priority for immediate testing or resource-intensive detailed

evaluation. However, when the estimates of exposure or dose to worker are higher than the TTC benchmark for a given Cramer class, then it requires additional focused evaluation of exposure and toxicity, just as has been done with flavoring substances (Kroes *et al.*, 2005; Munro *et al.*, 2008). For the occupational contaminants, the OTTC benchmarks for comparing with the worker exposure (dose) estimates were developed for the 5^{th}, 10^{th} or 25^{th} percentiles in this work. If the worker exposure (or dose) is below the chosen percentile value (5, 10 or 25 as the case may be), then there is no justifiable safety concern or priority to conduct more detailed testing to generate compound-specific data or give priority to that particular chemical relative to other candidate chemicals which may need to be tested. Even though the use of a lower percentile OTTC will ensure that there are less outliers, it will not serve the overall purpose of saving resources and efficiency in data-poor situations (NCM, 2005). Although choosing an appropriate percentile in order to screen out a given chemical, pragmatic considerations should be given to the type of worker population, context of chemical use and entity (ie, workplace/authority) that performs the screening.

3.5. Conclusion

In conclusion, this work has demonstrated the application of the TTC type analysis to the TLV data for airborne systemically acting organic chemicals. To our knowledge, this is the first attempt in applying the TTC principle for screening level occupational health risk assessment in the absence of relevant animal toxicology studies or occupational hazard data. The TTC principle and data developed in this study are useful for application with data-poor compounds, consistent with paradigm shift towards the 3R principles (ie, reduction, refinement, replacement of animal use) and use of intake estimates for screening level assessments of occupational contaminants.

3.6. Supplementary data

Supplementary data are available at *Toxicological Sciences* online.

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3.9. Figures

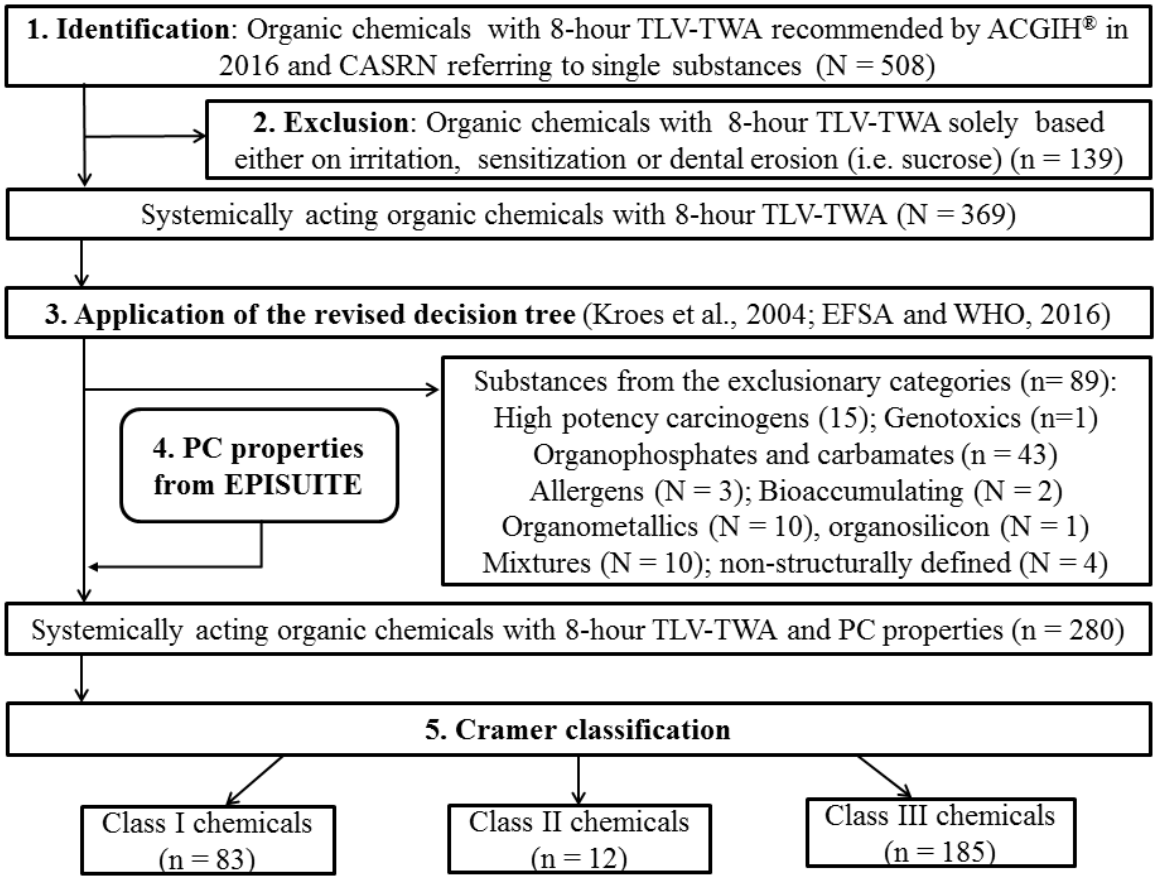

Figure 1. A flowchart describing the procedure used for selecting systemically acting noncarcinogenic organic chemical with OELs and their further assignment into the respective Cramer classes

(ACGIH, American Conference of Governmental Industrial Hygienists; CASRN; chemical abstract service register number; PC, physiochemical; PHB, polyhalogenated biphenyls; TLV-TWA, time weighted average threshold limit value).

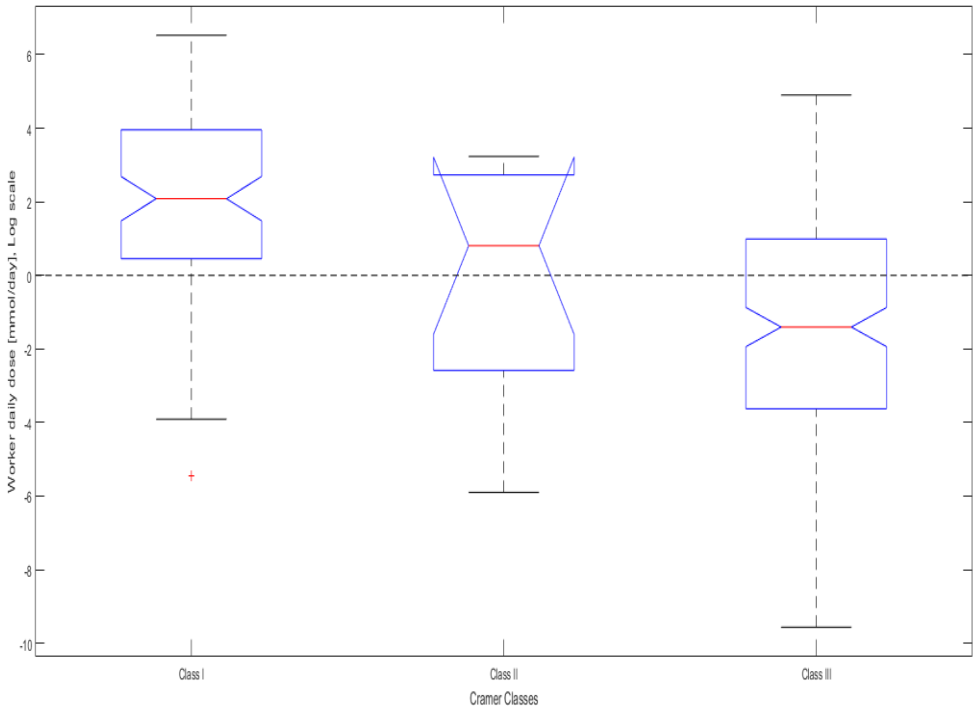

Figure 2. Boxplot of the distribution of the worker daily doses by Cramer class.

The boxes represent the 25th, 50th, and 75th percentiles of the distribution of the log values of the daily dose of chemicals belonging to Cramer classes I-III, respectively.

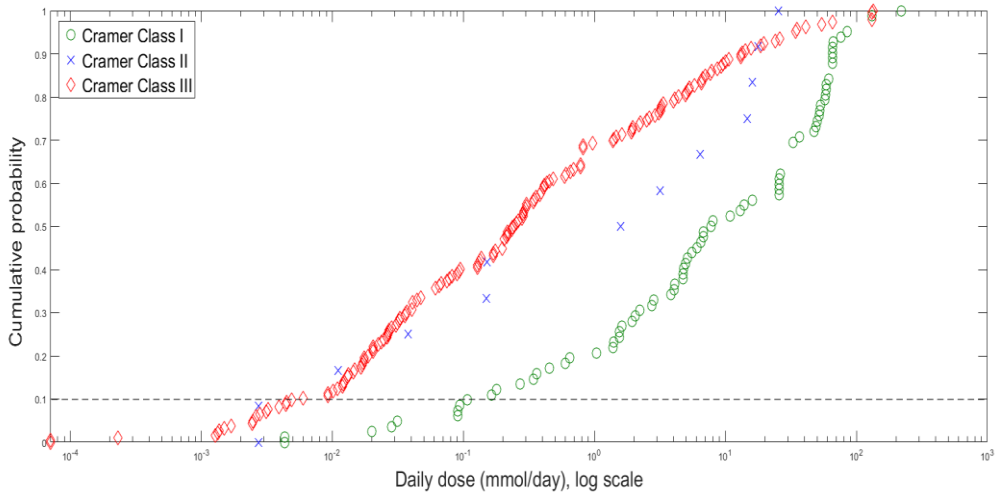

Figure 3. Cumulative density function of the worker daily doses for the 3 Cramer classes.

3.10. Tables

Table 1. Descriptive Statistics of the 8-h TWA-TLVs and the Worker Daily Doses for the Organic Chemicals as a Function of Cramer class

Cramer	n	8-h TLV-TWA (mg/m^3)					Worker Daily Dose (mmol/d) [a]				
Classes		GM	GSD	5^{th} p	Med	95^{th} p	GM	GSD	5^{th} p	Med	95^{th} p
I+II+III	280	13.47	23.17	0.10	11.14	1741.80	0.72	23.85	0.003	0.80	65.72
I	83	108.75	12.74	0.81	172.11	2950.90	6.63	11.63	0.07	8.04	131.18
II	12	12.40	21.20	0.04	36.46	296.19	0.82	20.10	0.004	2.38	24.67
III	185	5.31	21.74	0.08	5.90	895.24	0.26	19.09	0.003	0.25	34.48

[a]Exposure, 8 h/d, 5 d/wk. 8-h TLV-TWA, 8-h time weighted average threshold limit values; GM, geometric mean; GSD, geometric standard deviation; Med, median; p, percentile.

Table 2. Predicted and Experimental Human Blood:Air Partition Coefficients (P_{ba}) and PRF for a Set of 27 Chemicals From the Dataset

Name	CAS	Log P_{ba}[a]		PRF (%)[b]	
		Predicted	Exp	Predicted	Exp
1,1,1-Trichloroethane	71-55-6	0.53	0.50	37.97	26.00
Acetone	67-64-1	2.10	2.33	57.20	49.00
Acrylonitrile	107-13-1	2.31	**1.29**	59.21	52.00
Aniline	62-53-3	3.82	**4.02**	74.05	90.00
Carbon disulfide	75-15-0	0.70	0.30	41.61	40.00
Cyclohexanol	108-93-0	3.58	**3.09**	71.64	64.00
Dichloromethane	75-09-2	0.88	0.95	45.19	70.00
Dimethylformamide	68-12-2	4.32	**3.01**	78.94	81.00
Ethylbenzene	100-41-4	1.70	1.45	62.44	49.00
2-Ethoxyethanol	110-80-5	4.02	4.32	75.96	64.00
2-Ethoxyethyl acetate	111-15-9	3.29	1.45	68.83	57.00
Ethyl tert-butyl ether	637-92-3	1.03	1.07	48.54	33.00
2-Methoxyethyl acetate	110-49-6	3.34	4.52	69.32	76.00
Methanol	67-56-1	2.77	3.29	63.76	58.00
Methyl tert-butyl ether	1634-04-4	1.05	1.25	46.94	44.00
Methyl ethyl ketone	78-93-3	2.18	2.21	57.99	53.50
Methyl isobutyl ketone	108-10-1	2.25	2.10	74.01	60.00
m-Xylene	108-38-3	1.72	1.55	63.05	65.00
n-Hexane	110-54-3	0.31	0.07	33.26	23.00
Nitrobenzene	98-95-3	3.88	**2.87**	100	80.00
o-Xylene	95-47-6	1.71	1.55	62.78	65.00
Phenol	108-95-2	3.99	**4.55**	75.71	68.00
p-Xylene	106-42-3	1.71	1.55	62.70	65.00
Styrene	100-42-5	1.96	1.73	68.06	66.00
Tert-Amyl methyl ether	994-05-8	1.27	1.25	53.53	51.00
Tetrachloroethylene	127-18-4	1.05	1.09	48.81	61.00
Toluene	108-88-3	1.51	1.12	58.56	53.33

Exp, experimental.

[a]For the P_{ba}, the experimental values were obtained from the compilation by Buist et al. (2012) except those in bold which correspond to the calculated values from Jakubowski and Czerczak (2009).

[b]For the PRF, the experimental values represent the average of the range of experimental values reported for each chemical by Jakubowski and Czerczak (2009).

Table 3. ANOVA of the Worker Daily Doses of the Studied Organic chemicals

Kruskal-Wallis ANOVA Table					
Source	Sum Square	df	Mean Square	F-value	*p*-value
Groups	381048.5	2	190524.2	58.54	1.94657×10^{-13}
Error	1428661	276	5176.3		
Total	1809709.5	279			

df, degree of freedom.

Table 4. The OTTCs as a Function of Percentiles Obtained From the Distribution of TLVs of Systemically Acting Noncarcinogenic Chemicals

Cramer classes	OTTC (mmol/d)		
	5^{th} percentile	10^{th} percentile	25^{th} percentile
I	0.07	0.15	1.55
II	0.004	0.0085	0.09
III	0.003	0.0060	0.03

OTTC, occupational TTC.

Table 5. Application Domain of the Proposed Occupational Thresholds of Toxicological Concern

Cramer Classes	Application Domain [Min; Max]				
	8-h TLV-TWA (mg/m^3)	MW (g/mol)	$LogP_{ow}$ (unitless)	VP (Pa)	WS (g/l)
I	0.10; 9000	28.01; 278.35	-0.91; 4.76	$0.002; 4.19\times 10^{6}$	0.0004; 1000
II	0.04; 303.15	58.04; 328.46	-1.66; 8.55	$0.0004; 3.84\times 10^{4}$	$3.50\times 10^{-7}; 1000$
III	$0.002; 7.66\times 10^{3}$	40.07; 431.10	-2.82; 8.33	$8.90\times 10^{-10}; 2.49\times 10^{6}$	$1.60\times 10^{-7}; 1000$

Chapitre 4. A framework for application of quantitative property-property relationships (QPPRs) in physiologically based pharmacokinetic (PBPK) models for high-throughput prediction of internal dose of inhaled organic chemicals

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A framework for application of quantitative property-property relationships (QPPRs) in physiologically based pharmacokinetic (PBPK) models for high-throughput prediction of internal dose of inhaled organic chemicals

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Highlights

- An integrated QPPR-PBPK modeling framework to predict inhalation toxicokinetics.
- Tests with 40 chemicals in application domain and 249 from many structural features.
- Reality check of results and reliability based on sensitivity/uncertainty analyses.
- Discussion of the modeling framework usefulness for screening and prioritization.

Abstract

New generation of toxicological tests and assessment strategies require validated toxicokinetic data or models that are lacking for most chemicals. This study aimed at developing a quantitative property-property relationship (QPPR)-based human physiologically based pharmacokinetic (PBPK) modeling framework for high-throughput predictions of inhalation toxicokinetics of organic chemicals. A PBPK model was parameterized with QPPR-derived values for hepatic clearance (CL_h) and partition coefficients (P) [blood:air (P_{ba}) and tissue:air (P_{ta}) and tissue:blood (P_{tb})]. The model was initially applied to an evaluation dataset of 40 organic chemicals in the applicability domain, and then to an expanded dataset of 249 organic chemicals from diverse chemical classes. 'Batch' analyses were performed for rapid assessments of hundreds of chemicals. The simulations of inhalation toxicokinetics following an 8-h exposure to 1 ppm of each chemical were successful. The mean ratios of their predicted-to-experimental values were within a factor of 1.36 - 2.36 for P_{tb} and 1.18 for CL_h, for 80% of the chemicals in the evaluation dataset. The predicted 24-h area under the venous blood concentration-time curve (AUC_{24}) values were within the predicted envelopes obtained while using experimental values of P_{ba} and considering either no or maximal hepatic extraction. The reliability analysis (based on combined sensitivity and uncertainty analyses) indicated that AUC_{24} predictions for 55% of

the expanded dataset were moderately to highly reliable, with 46% exhibiting highly reliable values. Overall, the modeling framework suggests that molecular structure and chemical properties can together be effectively used to obtain first-cut estimates of the toxicokinetics of data-poor organic chemicals for screening and prioritization purposes.

Keywords: High-throughput toxicokinetics; hepatic clearance; PBPK modeling; Physiological pharmacokinetics; Quantitative property-property relationships.

4.1. Introduction

Animal-free human health risk assessments for occupational and environmental contaminants require species- and chemical-specific toxicokinetic models or data (e.g., internal dose) which are lacking in most cases (Creton et al., 2009; Bessems et al., 2014). To facilitate such assessments for emerging chemicals and interpret new generation of toxicity tests results, innovative and efficient approaches are essential. In this regard, it is relevant to develop high-throughput (HTP) modeling approaches for enabling the prioritization and/or screening-level risk assessments of data-poor chemicals (Chen et al., 2012). Such tools, by allowing the estimation of internal dose metrics, would enable the identification of lead chemicals or critical toxicokinetic endpoints (Creton et al., 2009; Chen et al., 2012). Several *in vitro* and *in silico* approaches, emerging as alternatives to the common animal-based toxicity tests (e.g., U.S. Tox21 and ToxCast programs) (MacGregor et al., 2001; Adler et al., 2011; Bessems et al., 2014; Wambaugh et al., 2015) require knowledge of pharmacokinetic parameters (e.g., plasma protein binding, volume of distribution and metabolic clearance) to facilitate *in vitro-in vivo* extrapolations (IVIVE) (Wetmore et al., 2012, 2013, 2015; Wambaugh et al., 2018). In this regard, physiologically based pharmacokinetic (PBPK) models are valuable quantitative tools that facilitate IVIVE as well as other essential extrapolations (Peters, 2008; Adler et al., 2011; Bessems et al., 2014; Krishnan, 2018).

Some investigators have implemented PBPK modeling frameworks for data-poor environmental chemicals to integrate data on pharmacokinetic determinants from HTP *in vitro* assays or quantitative structure-activity relationships (QSARs), including quantitative structure-property relationships (QSPRs) and quantitative property-property relationships (QPPRs) (Béliveau et al., 2005; Peyret and Krishnan, 2011; Wambaugh et al., 2015). The overall

applicability of these approaches to rapid, screening-level, PBPK model development is limited either because of the limited applicability domain (AD) of QSARs and QPPRs or due to the need for extensive chemical-specific *in vitro* experimentation.

Regarding the fundamental chemical-specific input parameters required for PBPK modeling, a number of QSARs and biologically-based algorithms or a combination thereof, have been developed for predicting blood:air (P_{ba}), tissue:air (P_{ta}) and tissue:blood (P_{tb}) of environmental chemicals and drugs, but with varying AD and levels of success (Poulin and Krishnan, 1996; Brightman et al., 2006; Schmitt, 2008; Peyret et al., 2010; Caldwell et al., 2012). In the case of biochemical constants (particularly metabolism rate and enzyme affinity), although considerable progress has been made by integrating HTP *in vitro* data within PBPK models, improved IVIVE approaches as well as analytical capacity to generate rapidly such data for new and emerging chemicals are still needed. Despite the efficiency and appeal associated with *in silico* approaches, much less progress has been made (Peyret and Krishnan, 2011; Kirchmair et al., 2015). More recently, Sarigiannis et al. (2017) have used artificial neural network technique to develop QSARs for the maximal velocity (V_{max}) and the Michäelis-Menten affinity constant (K_m) from Abraham's solvation equation parameters but with limited number of chemicals (n = 29). Peyret and Krishnan (2012) and Kirman et al. (2015) conducted multilinear regression analysis to propose QPPRs for intrinsic clearance ($CL_{int} = V_{max}/K_m$). While the AD of the former study ($r^2 = 0.796$) based on *in vivo* data was very narrow ($0.16 \leq Log\ P_{blood:water} \leq 2.49$; $1.09 \leq \text{Log } P_{ow} \leq 4.03$; $9.13 \leq$ ionization potential ≤ 11.28), the latter analysis did not improve the understanding of the variability across chemicals ($r^2 = 0.39$) even though it included additional data obtained in *in vitro* assays.

Considerable efforts have focused on developing QSARs and predictive models for hepatic and whole-body clearances of pharmaceuticals (Peach et al., 2012; Zakharov et al., 2012; Stepensky, 2013; Kirchmair et al., 2015; Lambrinidis et al., 2017). However, the transferability of the predictive models of metabolism for typical pharmaceuticals (mainly metabolized by CYP2D6, CYP3A4, CYP2C9, CYP1A2) to classical environmental chemicals (mainly metabolized by CYP2E1, CYP1A1, CYP1A2, CYP1B1, CYP3A4) is limited by known differences in key isozymes involved, their physicochemical properties, and extent of plasma protein binding (Bessems et al., 2014). Nonetheless, examples integrating databases on metabolism of both drugs and environmental contaminants continue to emerge, since the models can account for aspects such as lipophilicity differences and structural features. Thus, Arnot et al. (2014) used a dataset of 80% pharmaceuticals and 20% environmental chemicals to successfully develop QSARs for predicting human half-lives. Furthermore, Bois et al. (2017) used QSARs based on one-compartmental modeling of pharmaceuticals to derive estimates of elimination constants for computing human steady-state concentrations of environmental chemicals, primarily aromatase inhibitors (n = 86). However, neither clearance values nor volume of distribution (V_d) were calculated by these authors to facilitate integration within PBPK models.

Some impediments in using the existing QSARs for developing PBPK models have long been, among other factors, their limited AD and the lack of biological considerations. Under these circumstances, the application of QPPRs in PBPK models will lead to predictions associated with varying levels of uncertainty for the different subsets of data-poor chemicals. However, for screening and prioritization purposes, the focus should be on the level of confidence or reliability of QPPR-PBPK model outcomes as a function of not only the

uncertainty in QPPR-derived values of pharmacokinetic determinants but also the sensitivity of the PBPK model outputs (e.g., internal dose) to these QPPR-derived values. Such an approach, facilitating the efficient and focused use of QPPRs in PBPK modeling, has not yet been attempted.

Therefore, the aim of the current study was to develop a generic QPPR-PBPK modeling framework for providing high-throughput predictions of internal doses of organic chemicals in humans.

4.2. Materials and Methods

The overall framework consisted of (*i*) identifying QPPRs for model parameterization, (*ii*) predicting the molecular structure-based internal dose, and (*iii*) evaluating the reliability of the model outputs (Fig. 1).

4.2.1. Data compilation

To compute the P_{tb} (= P_{ta}/P_{ba}) for each chemical, the data on the following physicochemical properties were obtained using EPI Suite™ software, version 4.11 (U.S. Environmental Protection Agency, Washington, D.C., USA): molecular weight (*MW*), vapor pressure at 25°C (*VP*), *n*-octanol:water partition coefficient at 25°C (P_{ow}) and air:water partition coefficient at 37°C (P_{aw}).

For estimating the hepatic clearance (CL_h), the first-order total elimination rate constant (K_{el}) was estimated based on chemical structure with the ACD/Labs Percepta software, version 14.0.0 (Advanced Chemistry Development, Toronto, ON, Canada).

Due to limitations in the HENRYWIN module of EPI Suite™, the mean value of P_{aw} at 35°C and 40°C was calculated instead of direct estimation at 37°C for acetic acid, acetone,

chlorobenzene, dichloromethane, ethylene dichloride, methyl ethyl ketone and toluene. Likewise, all the heptane isomers were assigned the same K_{el} value. Further, to avoid potential computation issues, the experimental value of Log P_{ow} (= 0.05) was used instead of the predicted value (= 0.00) for 2-isopropoxyethanol. Also, the P_{aw} maximum value (= 7784) for perfluorobutyl ethylene was assigned to propylene dichloride. Finally, data on human physiology and P_{tb} were obtained from the peer-reviewed literature (Poulin and Krishnan, 1996; Tardif et al., 1997) (Supplemental material 1-Table 1) while P_{ta}, P_{ba}, V_{max} and K_m were used to compute P_{tb} and CL_h (Supplemental material 1-Table 2).

4.2.2. Dataset compilation

Two datasets of chemicals were compiled in this study. The first set (evaluation dataset) corresponded to 40 chemicals used for evaluating and integrating the QPPRs within PBPK model. These chemicals, obtained from Peyret and Krishnan (2012) and Sarigiannis et al. (2017), were selected based on the availability of empirical data on P_{tb} and CL_h (as detailed above). The second dataset (application dataset) consisted of 249 systemically-acting organic chemicals obtained from the TLV® database (ACGIH, 2016; Chebekoue and Krishnan, 2017) which represented a variety of structural features and chemical families (Supplemental material 6). Both datasets were compiled in SPSS© for Windows, Release 25 (SPSS, Chicago, IL, USA) along with their chemical-specific data on CASRN, K_{el}, Log P_{ow}, MW, P_{aw} and VP, estimated as detailed above (Supplemental material 2-Table1).

4.2.3. QPPR-based PBPK modeling

4.2.3.1. Model structure

A PBPK model previously applied to simulate the inhalation toxicokinetics of organic chemicals (Ramsey and Andersen, 1984; Béliveau et al., 2005) was used in this study. This model describes the adult human body as a set of four perfusion-limited tissue compartments (liver, adipose tissue, poorly perfused tissues (muscle and skin), and richly perfused tissues) interconnected by the systemic circulation and lungs (Fig. 1). The inhalation of chemicals was described based on rapid equilibration between the arterial blood and alveoli in the gas-exchange lungs with no significant metabolic or storage capacity. The tissue compartments, considered homogeneous and well-stirred, were characterized by their water and lipid content. Since the PBPK model aimed at providing first-cut estimates of toxicokinetics, the liver was assumed as the only eliminating and metabolizing organ with the metabolism described by a single metabolic pathway that follows a linear kinetic process (Bessems et al., 2014). Accordingly, the hepatic metabolism was determined by the CL_h. No specific target organ or tissue was identified in this generic PBPK model.

4.2.3.2. Integrated QPPR-PBPK modeling

The QPPR-PBPK model implemented in the current study allows to integrate input data on species-specific parameters (i.e., human physiology) along with chemical-specific parameters (i.e., volume of distribution and metabolic clearance). Whereas the human physiological parameters are generic parameters of this model (that are independent of the chemical to be simulated), the other input parameters such as the volume of distribution and the metabolic clearance have to be computed for each chemical. The QPPRs within the PBPK model facilitate their computation based on molecular structure and chemical properties (e.g., vapor

pressure, molecular weight, water solubility, Log P_{ow}). The fact that QPPRs are integrated within PBPK models provides a unique prediction and implementation environment bounded by physiological limits, such that QPPRs cannot operate to provide unrealistic toxicokinetic predictions independent of the physiological constraints of the PBPK model.

4.2.3.2.1. Model parameterization

4.2.3.2.1.1. Physiological parameters

In this model, the alveolar ventilation rate was set equal to the cardiac output (QC). The tissue blood flow rates were expressed as a fraction of QC whereas the volume of each tissue compartment was calculated as a proportion of the body weight (Supplemental material 1-Table 1).

4.2.3.2.1.2. Partition coefficients

The P_{tb} values were computed as the quotient of the QPPR-derived P_{ta} to P_{ba} (Supplemental material 1-Table 2). Although several QPPRs and QSARs exist for predicting animal and human P_{ba} (Abraham et al., 2005; Peyret and Krishnan, 2011), the human QPPR proposed by Buist et al. (2012) was chosen because of its pragmatic nature. This model was developed with a database of human experimental values for Log P_{ba} ranging from -1.42 (methane) to 4.52 (2-methoxyethanol). As such, the highest prediction value from Buist et al. (2012) was considered as the maximal value of the predicted Log P_{ba} in the current study (i.e., P_{ba} cutoff = Log 4.52).

The P_{ta} values at 37°C were estimated from information on the tissue-specific composition data (neutral lipids, phospholipids and water levels) along with the P_{aw} and $P_{vegetable\ oil:air}$ (P_{voa}) *as per* Poulin and Krishnan (1996). The latter in turn was computed by dividing the QPPR-derived $P_{vegetable\ oil:water}$ (Poulin and Haddad, 2012) by the P_{aw}. Given the dependence of

P_{ta} on P_{aw} and the greater uncertainty in P_{aw} predictions for chemicals with Log P_{aw} < -5 (Arnot et al., 2014), for chemicals with Log P_{aw} ≤ -4.71 (for carbon monoxide), the above-mentioned P_{ba} cutoff was not applied.

4.2.3.2.1.3. Metabolic rate constants

The available QPPRs for metabolic rate constants either exhibit very limited AD (Waller et al., 1996; Peyret and Krishnan, 2012) or have not been evaluated for integration within PBPK models (Arnot et al., 2014; Kirman et al., 2015). Recently, K_{el}, obtained from molecular structure information with the ACD/Labs software, has been used for computing steady-state blood concentrations (Bois et al., 2017). However, for integrating within PBPK models, this K_{el} can be converted to CL_h as follows:

$$\mathrm{CL_h} = \mathrm{V_d} \times \mathrm{K_{el}} \quad (1)$$

where K_{el}, first-order total elimination rate constant (h^{-1}) and V_d, apparent volume of distribution (L).

This conversion or adaptation of K_{el} from 1-compartment model to full-blown PBPK models has not yet been attempted. In order to overcome this obstacle, in this study, V_d was computed as follows:

$$\mathrm{V_d} = \mathrm{V_b} + \sum_1^4(\mathrm{V_{ti}} \times \mathrm{P_{tbi}}) \quad (2)$$

where V_b, volume of blood (L; 5.9% of body weight (Andersen et al., 1991)); V_{ti}, volume of each individual tissue compartment (L; expressed as blood-equivalent volume); and P_{tbi}, tissue:blood partition coefficient for individual tissue compartment i (unitless).

4.2.3.2.2. Model simulations

The PBPK model consisted of single or groups of tissues represented by a set of mass-balance ordinary differential equations (MBDEs) as well as algebraic expressions (Supplemental material 4). All the MBDEs were coded in MATLAB^{TM} software (The MathWorks, Inc., Natick, MA, USA) and solved by numerical integration using the Matlab solver *ode15s*. The PBPK model code files can be obtained by contacting one of the authors. The same model was used to simulate two measures of internal dose, namely the CV profile and the 24-h area under the venous blood concentration *vs* time curve (AUC_{24}), for each chemical in the evaluation dataset (40 chemicals) and application dataset (249 chemicals). Instead of using V_{max} and K_m, the current study used the QPPR-derived CL_h to compute the rate of the amount metabolized (RAM) (Ramsey and Andersen, 1984), as follows:

$$\mathrm{RAM} = \mathrm{CL_h} \times \mathrm{CA} \quad (3)$$

where CA = arterial blood concentration (mg. L^{-1}).

To perform a reality check of the QPPR-based predictions, PBPK modeling for each chemical in the evaluation dataset was also conducted considering the theoretical limits of hepatic metabolism (i.e., CL_h = 0 or Q_l). Since CL_h is a function of hepatic blood flow (Q_l) and hepatic extraction ratio (E), the RAM was computed as follows (Poulin and Krishnan, 1999):

$$\mathrm{RAM} = \mathrm{Ql} \times \mathrm{E} \times \mathrm{CA} \quad (4)$$

Thus, the envelopes of toxicokinetic profiles and ranges of AUCs were predicted considering E = 0 or 1.

All the simulations were conducted in 'batch' mode for an exposure to 1 ppm for 8 h. The inhaled concentration in ppm unit was converted to mg. L^{-1} for input to the model as follows:

$$\mathrm{C_{inh}}\ (\mathrm{mg.L^{-1}}) = \frac{\mathrm{C_{inh}\ (ppm)} \times \mathrm{MW}}{24450} \quad (5)$$

4.2.3.3. Model evaluation

For evaluating the usefulness of the QPPR-PBPK modeling framework in predicting AUC, this study relied on a two-tier strategy: (*i*) assessment of the extent of concordance between model predictions and known theoretical limits for chemicals in the evaluation dataset and (*ii*) assessment of the reliability of the predicted AUCs for chemicals within the application dataset.

Specifically, in the first tier, the predicted P_{tb} (= P_{ta}/P_{ba}) and CL_h (=V_{max}/K_m) were first compared with their corresponding empirical data (Supplemental material 3-Table 1). Secondly, the predicted AUC_{24}s were compared with PBPK modeling results obtained using empirical values of P_{ba} (Abraham et al., 2005) and plausible boundaries of metabolism (E = 0 or 1) for each of the 40 chemicals. For the second tier, the model was used to simulate the inhalation kinetics of 249 additional chemicals, for which no experimental kinetic data or parameters were available.

While implementing the above strategy, it becomes imperative to assess the level of confidence in using QPPRs in PBPK models to make predictions of AUC. Accordingly, by adopting the WHO (2010) framework for reliability analyses of PBPK models, a matrix of (*i*) the level of uncertainty in QPPR-derived P_{ba} and CL_h values and (*ii*) the sensitivity of PBPK outputs of AUC_{24} to these predicted input parameters, was developed. Whereas the uncertainty in QPPRs was assessed qualitatively, the sensitivity of the PBPK model output was assessed quantitatively.

Regarding the QPPR-derived P_{ba}, the high, medium or low level of uncertainty depended as to whether a chemical is within the AD of the QPPR based on consideration of one, two or all of the following characteristics: Log P_{ow}, Log *VP* and *MW* (Buist et al., 2012). For example, when all three parameters for a given chemical are within the AD of the QPPR model, then the

predicted P_{ba} is considered to display low uncertainty. In contrast, when only one parameter is within the AD, then the predicted P_{ba} is considered highly uncertain. Likewise, the qualitative uncertainty of the QPPR-derived CL_h was associated with the Log P_{ow} as follows: Log $P_{ow} > 5$ (high uncertainty); $2 \leq$ Log $P_{ow} \leq 5$ (medium uncertainty); Log $P_{ow} < 2$ (low uncertainty), since the datasets used by ACD/Percepta software contain drug-like substances rather than highly lipophilic environmental contaminants. Regardless of the uncertainty associated with estimates of QPPR-derived parameters, the impact of such parameters on model outputs is critical. In this regard, sensitivity analyses were performed to determine the chemicals for which the QPPR-derived P_{ba} or CL_h had the greatest impact on the predicted AUC_{24}s. Therefore, for each chemical in the application dataset, by simulating the impact on AUC_{24} of a 10% increase over the baseline value of each input parameter, a normalized sensitivity coefficient was calculated (Tardif et al., 2002).

The results of this evaluation were then organized into 3 categories: (*i*) chemicals with predicted AUC_{24} values that are highly reliable; (*ii*) chemicals with predicted AUC_{24} values that are moderately reliable; and (*iii*) chemicals with predicted AUC_{24} values considered less reliable.

4.3. Results

4.3.1. QPPR-derived chemical specific parameters

For the evaluation dataset, the QPPR-based predictions of P_{tb} values were, on average, within a factor of 1.36-2.36 of the experimentally-derived values. The predicted-to-experimental values (mean ± SD; range) for P_{fb}, P_{sb} and P_{lb} were 2.36 (± 3.95; range: 0.03-18.05); 1.60 (± 1.95; range: 0.04-8.37); 1.36 (± 1.86; range: 0.04-8.63), respectively (Table 1). Overall, at least

70% of chemicals had P_{tb} predicted values within a factor of 2 of experimental data whereas poor predictions (i.e., mean ratio ≤ 0.1) were consistently obtained for 2-methylpentane, heptane, n-hexane, and octane, although their predicted P_{ba} values were within factors of 1.2-3.9. Also, the calculated ratios for 1,2-dichloroethane and 1,4-dioxane were consistently higher than 5 for all the P_{tb} (Table 1).

Regarding CL_h, the average ratio of the predicted-to-experimental data was 1.18 (± 1.73; range: 0.04-9.66) for the entire set. For 36 out of 40 chemicals, the QPPR-derived values were within a factor of 2. Of these chemicals, nine had a predicted-to-experimental ratio of less than 0.3 (bromodichloromethane, chloroform, dibromochloromethane, dichloromethane, ethylene, furan, n-hexane, octane, propylene). Three chemicals (1,4-dioxane, hexachloroethane and trichloroethylene) had predicted CL_h within a factor of 2-5 of the experimental values, whereas tetrachloroethylene, a poorly metabolized chemical, exhibited the largest discrepancy of about an order of magnitude (Table 1).

4.3.2. QPPR-PBPK modeling

The QPPR-derived partition coefficients and CL_h obtained as above (Table 1), along with the human physiological data (Supplemental material 1-Table 1), were then provided as input in the PBPK model to simulate the CV and AUC_{24} of each chemical following inhalation exposure to 1 ppm for 8 h (Supplemental 5-Fig. 1). Simulations were also obtained by setting the liver extraction ratio (E) to 1 or 0, to generate the theoretical envelope of predictions. For 20% of chemicals (1,1-dichloroethylene; 2-methylpentane; ethylene; n-hexane; isoprene; methyl chloride; propylene; vinyl chloride), the ratio of AUC reflective of complete *vs* no hepatic extraction (i.e., AUC_{E1}/AUC_{E0}) was ≤ 2; > 5 for 9 chemicals while it ranged between 2

and 5 for all other chemicals except 1,4-dioxane, bromoform and dibromochloromethane for which it was ≥10 (Table 2).

The use of QPPR-based values of CL_h, P_{ba} and P_{tb} in the PBPK model resulted in AUC_{24} values and toxicokinetic profiles that were on or within the boundaries (i.e., minimum and maximum) obtained by setting E = 1 or 0, for all the chemicals in the initial dataset except 1,1-dichloroethylene, 1,2-dichloroethylene (cis-), 2-methylpentane, benzene, halothane, hexane (n-), isoprene and octane.

The QPPR-PBPK model was then used to simulate the toxicokinetics of 249 additional chemicals (Supplemental material 6). Fig. 2 displays the kinetic profiles of a subset of 20 randomly selected chemicals from this expanded dataset, reinforcing the observation that for most of the chemicals the predicted profile was on or within the *a priori* boundaries determined with maximal or no hepatic extraction.

4.3.3. Performance and reliability analyses of the QPPR-PBPK model

The reliability of QPPR-PBPK model predictions of internal dose was assessed for two chemical-specific input parameters, namely P_{ba} and CL_h. The reliability of predicted AUC_{24} was high for 56% chemicals of the dataset, moderate for 34% and less for 10%, while considering the uncertainty associated with P_{ba} (Table 3a). Similarly, the consideration of the uncertainty in QPPR-derived CL_h along with the sensitivity of AUC_{24} to this input parameter, led to model output that were highly reliable for 66%, moderate for 27%, and less reliable for 7% of the chemicals in the expanded dataset (Table 3b).

Overall, when accounting for the uncertainties associated with QPPRs for both P_{ba} and CL_h, a combined analysis showed that the proposed approach would enable AUC_{24} predictions that are moderate to highly reliable for 55% of the chemicals (Table 3c): $28.01 \leq MW \leq 393.73$;

-2.82 ≤ Log P_{ow} ≤ 4.74; -8.83 ≤ Log VP ≤ 6.40; -10.94 ≤ Log P_{aw} ≤3.89 (median = -2.2). On the contrary, 11 chemicals from the expanded database, mostly chlorinated as well as hydrogenated terphenyls, were associated with predictions of AUC_{24} that were considered less reliable (Table 3c).

4.4. Discussion

Toxicokinetic data and models play a key role in scientifically-sound characterization of dose-response relationships, and interpretation of human biomonitoring data (Creton et al., 2009). There is an increasing emphasis in using toxicokinetic models in the context of evolving paradigm of toxicity testing and risk assessment. As such, the development of HTP approaches both for the derivation of toxicokinetic parameters as well as for the construction of PBPK models has attracted considerable attention in the scientific community (Chen et al., 2012). So far, there have been few successful attempts to develop predictive models of oral pharmacokinetics of pharmaceuticals and inhalation toxicokinetics of environmental contaminants, based on HTP results (MacGregor et al., 2001; Corley et al., 2003; Peyret et al., 2010; Gombar and Hall, 2013; Bessems et al., 2014; Strope et al., 2018). To interpret new generation of toxicity studies, Wambaugh et al. (2015, 2018) developed an HTP toxicokinetic framework for the oral and iv routes, based on both IVIVE (for CL_{int} and plasma protein binding) and QSARs (for partition coefficients and transporter affinity). The current study fills a data gap regarding inhalation toxicokinetics of occupational contaminants and provides proof-of-applicability of structure-property and property-property relationships for developing human PBPK models.

Molecular structure-based PBPK models represent valuable tools in an animal-free human health risk assessment framework. Considering the thousands of data-poor chemicals in the

occupational environment, the development of such models can facilitate the understanding of their uptake and disposition, at least in the context of screening and prioritization to collect additional data. The primary bottle-neck in the development of inhalation human PBPK models for such chemicals relates to the knowledge of chemical-specific parameters. While several studies have focused on QSAR and QPPR development to predict partition coefficients (Béliveau et al., 2005; Lu et al., 2016), the metabolic clearance in turn has frequently been scaled within human PBPK models using animal data or IVIVE approaches (Wambaugh et al., 2015, 2018). However, the integration of QPPR-derived metabolic clearance in PBPK models has poorly been explored. Generally, the use of QSPRs and QPPRs in PBPK model development has long been limited by the inadequacy of their applicability domains (Adler et al., 2011; Peyret and Krishnan, 2011; Bessems et al., 2014). However, one way of facilitating their broader use for screening and prioritization purposes would be to focus not just on QPPR prediction uncertainties but also on the sensitivity of the PBPK model output to such uncertainties. More specifically, a joint analysis of these two critical aspects could help gauge reliability of PBPK model output for purpose-specific end-use (WHO, 2010). In line with this perspective, the current study has developed a human PBPK modeling framework that on one hand relies entirely on published QPPRs to predict the chemical-specific input parameters (i.e., P_{tb} and CL_h), and on the other hand combines uncertainty and sensitivity analyses to evaluate the reliability of the internal dose predictions (i.e., AUC_{24}). In this study, the QPPR predictions of toxicokinetic determinants were bounded by the plausible boundaries of values based on biological or practical considerations. For example, any QPPR-derived estimate of CL_h greater than the biologically-plausible maximal value (i.e., hepatic blood flow rate), was set equal to that maximum. Similarly, the predicted P_{ba} was constrained not to exceed the P_{ba} cutoff, even though

values of P_{ba} exceeding this maximum will not directly influence the inhalation toxicokinetics because their kinetics will be ventilation-limited. Overall, the results demonstrated that even if the QPPR-derived input parameter values were less than optimal for certain chemicals, the AUC_{24}s were reliable when such parameters were not the most sensitive or critical input of the model. In this regard, the reliability analyses demonstrated that for most chemicals, the predicted molecular structure-based AUC_{24}s were reliable and within the boundaries defined by the theoretically-plausible minimal and maximal values of hepatic extraction. In their analyses, Wambaugh et al. (2018) also reported that reasonable predictions of internal dose metrics could be obtained despite the under-estimation of the metabolic clearance for certain chemicals.

The current study for the first time, by using peer-reviewed algorithms and emphasizing on the reliability of model outputs, enabled AUC_{24} predictions for a large dataset of data-poor chemicals that belong to a variety of chemical families with diverse structures (Supplemental material 2 and 6). Furthermore, this study has illustrated the use of QPPR-derived V_d to estimate CL_h from K_{el} representing first-order conditions. Even though QPPR-derived half-lives and K_{el} have previously been reported by other authors (Arnot et al., 2014; Bois et al., 2017), such parameters have not been integrated within PBPK models as attempted in the current study. Furthermore, the current study compared the QPPR-PBPK model predictions with the range of AUC_{24}s obtained considering theoretical limits of hepatic metabolism, thus ensuring a reality check of the resulting predictions.

The lack of experimental data for new chemicals was addressed in the current study through the use of a combined uncertainty and sensitivity analysis. In this regard, Lu et al. (2016) constructed a knowledgebase of PBPK models in relation to pharmacokinetically-relevant molecular descriptors, such that exact matches, close analogues, or non-analogues of the target

chemical can be identified from the literature. Subsequently, the input parameters, model equations, or experimental data relevant to existing models for these chemicals and their analogues were used to guide the construction and validation of PBPK models for other chemicals. Overall, Lu et al. (2016) used the chemical structure and descriptor information at a global approach to select models, whereas the current study focused on QPPRs for individual input parameters of the PBPK model.

The overall limitations of the methodology used in this study relate to the use of a single set of physiological parameters, single QPPR for each input parameter (i.e., volume of distribution and metabolic clearance) and single exposure route (i.e., inhalation). While Monte Carlo simulation approach can be implemented in this framework to account for distribution of physiological parameters (e.g., Bois et al. (2010)), a consensus QPPR modeling approach can be used if several credible individual predictive models are considered relevant for integration within PBPK models (Abshear et al., 2006). Furthermore, the simple screening-level PBPK modeling framework used in this study did not include more complex phenomena such as characterization of tissue-blood barriers, diffusion-limited uptake of larger molecules, ionization of molecules in the various physiological compartments, and temporal change in input parameters. These aspects can be additionally accounted for with appropriate data.

Furthermore, only the inhalation route was accounted for in the current study, as the chemicals in the dataset are occupational toxicants. Nonetheless, the proposed QPPR-PBPK modeling framework is applicable to other routes of exposure. For example, if the oral route is of interest, then the inclusion of a mass-balance equation to describe the amount absorbed as a function of time should be included, with consideration of QPPRs for route-specific parameters (e.g., oral absorption rate constant, oral bioavailability). Even though the current application of

the proposed modeling framework focused on occupational toxicants, it can also be applied to simulate environmental exposure to airborne toxicants. In that case, all one has to do is to account for difference in duration of exposure (e.g., 8 h versus 24 h) in the PBPK model, since all the other parameters will remain the same. Specifically, the QPPRs for the partition coefficients and the metabolic parameters used in the current study are applicable to all exposure scenarios in the first order range. Except for situations involving very high exposure levels that may cause the saturation of protein binding and metabolic enzyme sites (e.g., accidents, spills), the QPPR-PBPK model proposed here can be used for obtaining first-cut estimates of the toxicokinetics of environmental chemicals along with a notion of reliability associated with such predictions. Moreover, when applying the framework to simulate dose metrics at population level, the distributions of the physiological parameters may be included within the PBPK model to enhance the implementation of a probabilistic approach.

4.5. Conclusion

The high-throughput QPPR-PBPK modeling framework presented in this manuscript constitutes a potentially useful tool for predicting the inhalation toxicokinetics of data-poor chemicals, along with the confidence level in the outputs. The integrated modeling approach coupled with a reliability analysis as developed in this study represents a way forward in using the existing QPPRs for PBPK model development, and for predicting the toxicokinetics of data-poor organic chemicals. Until more robust QPPRs with broad applicability domains are developed for generating input parameters for PBPK models, the strategy developed and implemented in this study would facilitate (*i*) the prioritization of chemicals for which experimental data would be desirable and (*ii*) the application of toxicokinetics in screening-level assessments of airborne organic chemicals lacking data on internal dose in humans.

4.6. Disclaimer and acknowledgements

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4.7. Conflicts of interest

The authors have no competing interests to declare.

4.8. Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2018.10.041

4.9. References

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4.10. Figures

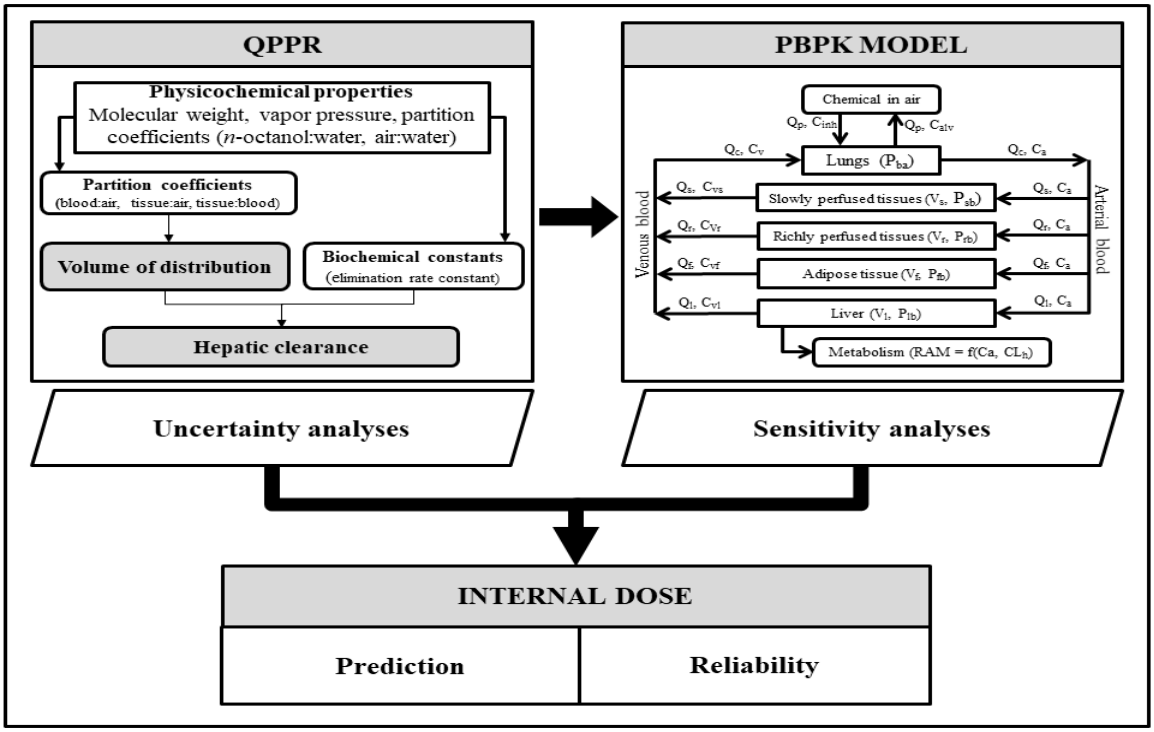

Fig. 1. Quantitative property-property relationships (QPPRs)-based human physiologically based pharmacokinetic (PBPK) modeling framework proposed in the current study.

The panel in the top right corner displays the conceptual representation of the PBPK model for organic chemicals. The chemical input to the system is via inhalation. Ca, arterial concentration; C_{alv}, alveolar concentration; C_{inh}, inhaled concentration; C_V, venous blood concentration; C_{vt}, concentration in venous blood leaving the corresponding tissue t (f, adipose tissue; l, liver; r, richly perfused tissues; s, slowly perfused tissues); CL_h, hepatic clearance; P_{ba}, blood:air partition coefficient; P_{tb}, tissue:blood partition coefficient for tissue t; Q_p, alveolar ventilation; Q_c, cardiac output; Q_t, blood flow rate of the corresponding tissue t; RAM, rate of amount metabolized.

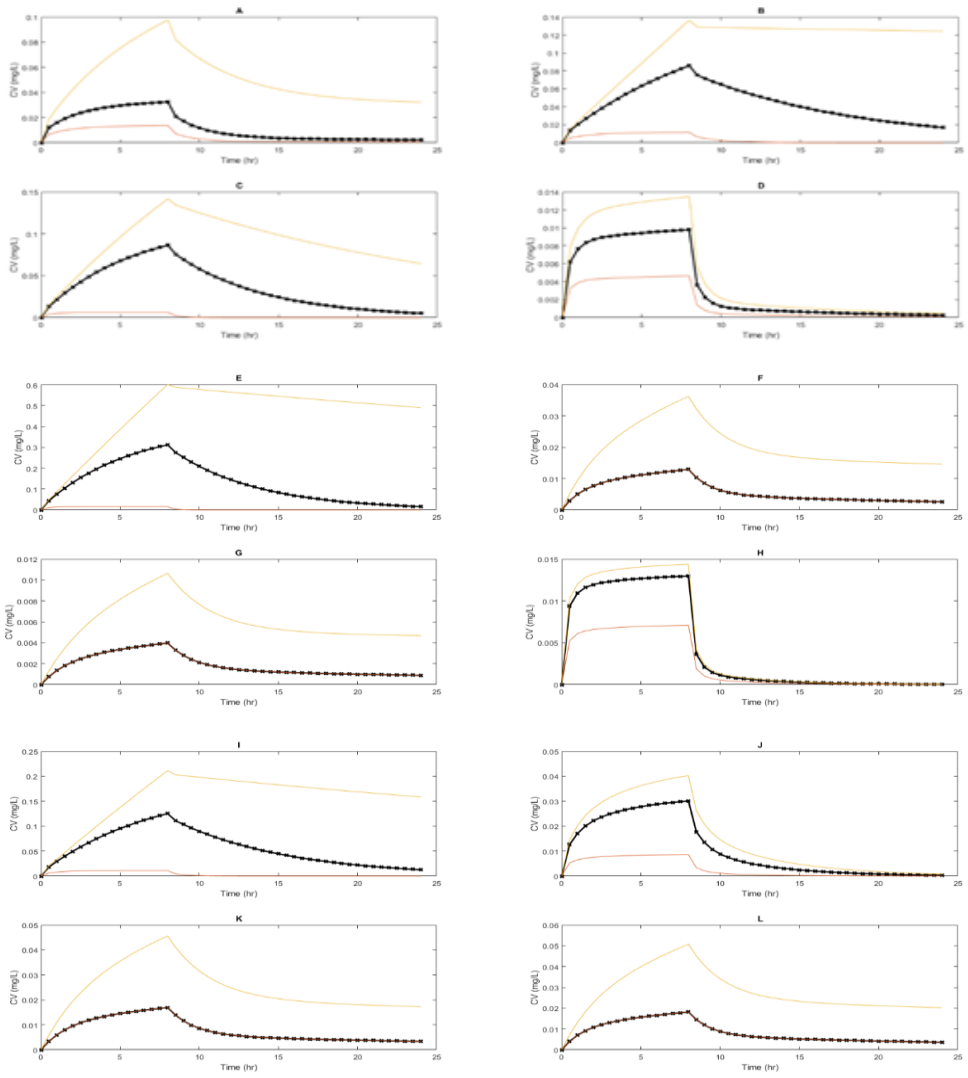

Fig. 2. PBPK model simulations of human venous blood concentration versus time curves of 20 chemicals (from the dataset of chemicals used for the expansion of the applicability domain), following an 8-h inhalation exposure to 1 ppm.

The lines with the crosses were obtained using the QPPR-derived P_{ba} and CL_h in the PBPK model whereas the plain solid lines correspond to predictions obtained by setting E equals to 1 (lower solid lines) or 0 (upper solid lines) in the PBPK model. A, methyl-naphthalene; B, 2,4-pentadione; C, acrylonitrile; D, allyl chloride; E, n-butyl glycidyl ether; F, dibutyl phthalate; G, dimethylacetamide; H, enflurane; I, epichlorohydrin; J, ethyl tert-butyl ether; K, heptachlor epoxide; L, Iodoform; M, n-isopropylaniline; N, p-nitrochlorobenzene; O, pentachlorophenol; P, propylene glycol dinitrate; Q, tetrahydrofuran; R, tetramethyl succinonitrile; S, vinyl acetate; T, vinylidene fluoride.

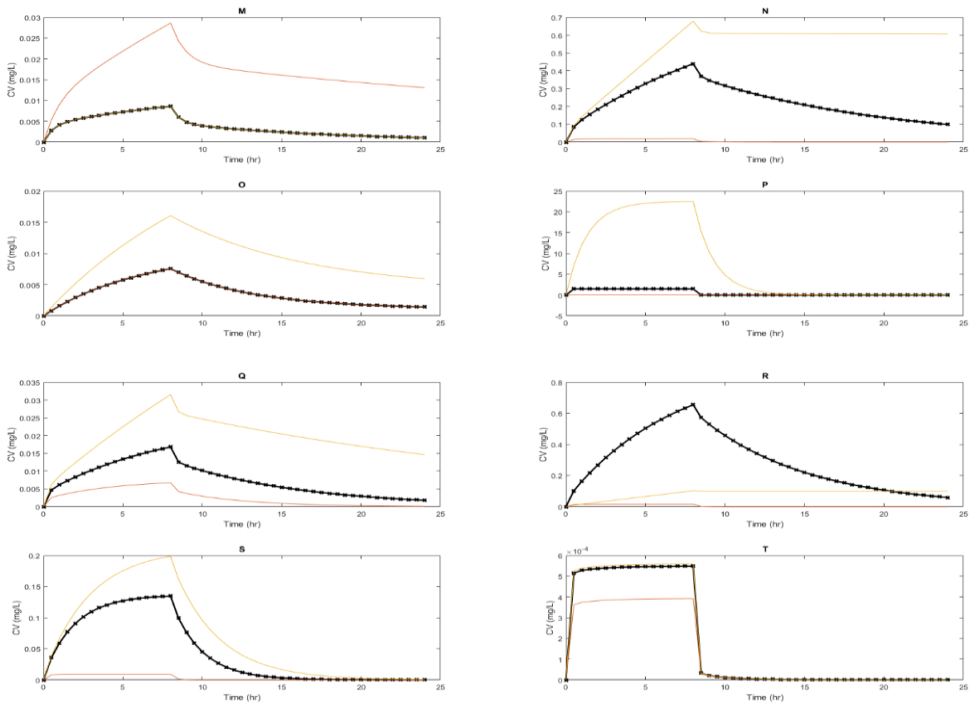

Fig. 2. (*continued*).

4.11. Tables

Table 1. Predicted and experimental values for the physicochemical and biochemical parameters of the 40 organic chemicals in the evaluation dataset[a].

Chemicals	*Kel* (min^{-1})	V_d (L/Kg)	Log P_{fb} (unitless)		Log P_{sb} (unitless)		Log P_{lb} (unitless)[b]		Log CL_h (L/h)[c]	
			Exp[d]	Pred	Exp[d]	Pred	Exp[d]	Pred	Exp	Pred
1,1,1,2-tetrachloroethane	1.60×10^{-3}	40.65	1.75	2.26	0.26	0.94	0.55	1.04	1.70	1.90
1,1,2,2-tetrachloroethane	1.90×10^{-3}	9.73	1.53	1.63	0.06	0.36	0.33	0.45	1.80	1.89
1,1,2-trichloroethane	2.00×10^{-3}	13.51	1.40	1.76	-0.02	0.53	0.20	0.61	1.75	1.90
1,2,4-Trimethylbenzene	1.60×10^{-3}	17.33	2.04	1.89	0.32	0.56	0.64	0.66	1.79	1.90
1,1-Dichloroethane	2.00×10^{-3}	3.01	1.27	1.09	-0.03	-0.07	0.09	0.00	1.86	1.40
1,2-Dichloroethane	2.10×10^{-3}	17.52	1.01	1.87	-0.24	0.68	-0.18	0.75	1.78	1.90
1,1-Dichloroethylene	1.90×10^{-3}	6.77	1.64	1.47	0.39	0.21	0.50	0.30	1.88	1.73
1,1-Dichloroethylene (cis-)	2.00×10^{-3}	10.67	1.13	1.66	-0.20	0.44	-0.05	0.51	1.68	1.90
1,1-Dichloroethylene (trans-)	2.00×10^{-3}	10.67	1.18	1.66	-0.15	0.44	0.00	0.51	1.85	1.90
1,4-Dioxane	2.20×10^{-3}	2.84	-0.64	0.23	-0.37	0.55	-0.37	0.54	0.77	1.42
2-Methylpentane	2.20×10^{-3}	1.50	2.33	0.81	0.85	-0.51	1.04	-0.41	1.19	1.14
Benzene	2.00×10^{-3}	2.44	1.82	1.01	0.40	-0.21	0.56	-0.14	1.82	1.31
Bromochloromethane	2.10×10^{-3}	3.14	0.18	1.08	0.18	0.06	0.25	0.10	1.83	1.44
Bromodichloromethane	2.00×10^{-3}	2.15	-0.33	0.93	-0.33	-0.18	0.07	-0.12	1.88	1.26
Bromoform	2.10×10^{-3}	3.86	0.04	1.20	0.04	0.03	0.30	0.10	1.88	1.53
Carbon tetrachloride	1.50×10^{-3}	5.02	2.13	1.34	0.24	0.05	0.73	0.14	1.35	1.50
Chloroethane	1.80×10^{-3}	3.57	1.02	1.15	-0.08	0.06	-0.09	0.11	1.86	1.43
Chloroform	2.00×10^{-3}	2.04	1.58	0.90	0.21	-0.17	0.36	-0.12	1.84	1.23
Dibromochloromethane	1.90×10^{-3}	2.30	1.57	0.97	0.04	-0.18	0.39	-0.11	1.88	1.26
Dibromomethane	2.00×10^{-3}	3.03	1.34	1.08	0.00	0.01	0.14	0.06	1.85	1.41
Dichloromethane	1.80×10^{-3}	2.20	1.15	0.91	-0.10	-0.07	0.08	-0.02	1.75	1.22
Ethylbenzene	1.70×10^{-3}	6.54	1.75	1.46	-0.03	0.14	0.48	0.24	1.68	1.67
Ethylene	1.80×10^{-3}	1.37	0.94	0.68	0.47	-0.25	0.31	-0.21	1.87	1.02
Furan	1.90×10^{-3}	0.38	0.99	-0.27	-0.19	-0.50	-0.05	-0.50	1.89	0.48
Halothane	8.10×10^{-4}	15.55	1.65	1.83	0.46	0.56	0.38	0.65	1.88	1.72
Hexachloroethane	1.40×10^{-3}	13.01	1.63	1.76	0.13	0.44	0.43	0.54	1.48	1.88
Heptane	1.90×10^{-3}	2.35	2.31	1.01	0.80	-0.31	0.76	-0.22	1.40	1.27
Hexane (n-)	2.10×10^{-3}	1.32	2.11	0.75	0.80	-0.57	0.81	-0.47	1.90	1.07
Isoprene	1.90×10^{-3}	7.68	1.14	1.53	0.18	0.23	0.14	0.32	1.86	1.79
Methyl chloride	1.90×10^{-3}	2.54	0.01	0.92	-0.08	0.11	-0.22	0.14	1.64	1.31
Octane	1.40×10^{-3}	0.97	1.76	0.61	0.32	-0.72	0.80	-0.62	1.44	0.76
Pentachloroethane	1.40×10^{-3}	28.05	1.78	2.10	0.28	0.78	0.57	0.87	1.76	1.90
Propylene	2.10×10^{-3}	1.40	1.07	0.74	0.10	-0.39	0.04	-0.33	1.64	1.09
Styrene	1.80×10^{-3}	7.40	1.70	1.51	0.00	0.20	0.43	0.30	1.84	1.75
Tetrachloroethylene	1.40×10^{-3}	10.65	2.20	1.67	0.89	0.36	0.83	0.45	0.81	1.80
Toluene	1.80×10^{-3}	4.01	1.97	1.24	0.53	-0.05	0.67	0.04	1.84	1.48
Trichloroethylene	1.80×10^{-3}	9.38	1.85	1.61	0.37	0.32	0.55	0.41	1.14	1.85
Vinyl chloride	1.80×10^{-3}	3.88	1.24	1.19	0.26	0.08	0.14	0.14	1.84	1.47
Xylene (m-)	1.70×10^{-3}	7.59	1.89	1.53	0.48	0.21	0.48	0.30	1.79	1.73
Xylene (o-)	1.70×10^{-3}	11.21	1.86	1.70	0.41	0.38	0.70	0.47	1.86	1.90

CASRN, Chemical Abstract Service Register Number; CL_h, hepatic clearance; V_d, apparent volume of distribution; K_{el}, elimination rate constant; P_{fb}, fat tissue:blood partition coefficient; P_{lb}, liver:blood partition coefficient; P_{sb}, slowly perfused tissues:blood partition coefficient; Exp, experimental; Pred, predicted.

[a]The following 27 chemicals (CASRN and name) from the evaluation dataset were removed when compiling the application dataset: 79-34-5 (1,1,2,2-tetrachloroethane); 79-00-5 (1,1,2-trichloroethane); 75-34-3 (1,1-dichloroethane); 156-59-2 (1,2-dichloroethylene (cis)); 156-60-5 (1,2-dichloroethylene (trans)); 123-91-1 (1,4-dioxane); 107-83-5 (2-methylpentahe); 75-25-2 (bromoform); 74-97-5 (chlorobromomethane); 67-66-3 (chloroform); 75-09-2 (dichloromethane); 100-41-4 (ethylbenzene); 75-00-3 (ethyl chloride); 74-85-1 (ethylene); 107-06-2 (ethylene dichloride); 151-67-7 (halothane); 67-72-1 (hexachloroethane); 142-82-5 (heptane); 110-54-3 (n-Hexane); 74-87-3 (methyl chloride); 115-07-1(propylene); 100-42-5 (styrene); 127-18-4 (tetrachloroethylene); 108-88-3 (toluene); 75-35-4 (vinylidene chloride); 108-38-3 (m-xylene); 95-47-6 (o-xylene).

[b]P_{lb}: values set equal to those for rapidly perfused tissues.

[c]CL_h was calculated as $CL_{int}/(CL_{int}+Q_l)$, with $CL_{int} = V_{max}/K_m$. Q_l was calculated considering a reference human cardiac output of 5.2 L/h, with 26% of this amount flowing into the liver (Brown et al., 1997). The experimental data on V_{max} and K_m were obtained from the peer-reviewed literature (see Supplemental material).

[d]The experimental data of P_{lb} were obtained from the peer-reviewed literature (see Supplemental material).

Table 2. Predicted dose metrics for 40 organic chemicals from the evaluation set.

Chemical	AUC_{24} (mmol/L.h)		
	CL_h[a]	E_1[b]	E_0[b]
1,1,1,2-Tetrachloroethane	6.01×10^{-4}	6.57×10^{-4}	2.98×10^{-3}
1,1,2,2-Tetrachloroethane	7.94×10^{-4}	7.83×10^{-4}	6.49×10^{-3}
1,1,2-Trichloroethane	7.21×10^{-4}	7.03×10^{-4}	3.85×10^{-3}
1,2,4-Trimethylbenzene	7.38×10^{-4}	6.87×10^{-4}	3.37×10^{-3}
1,1-Dichloroethane	1.33×10^{-3}	4.97×10^{-4}	1.47×10^{-3}
1,2-Dichloroethane	6.56×10^{-4}	6.45×10^{-4}	2.84×10^{-3}
1,1-Dichloroethylene	3.43×10^{-4}	1.51×10^{-4}	2.48×10^{-4}
1,2-Dichloroethylene (cis-)	4.78×10^{-4}	6.08×10^{-4}	2.46×10^{-3}
1,2-Dichloroethylene (trans-)	4.78×10^{-4}	5.05×10^{-4}	1.57×10^{-3}
1,4-Dioxane	3.09×10^{-3}	9.29×10^{-4}	2.91×10^{-2}
2-Methylpentane	4.60×10^{-4}	8.61×10^{-5}	1.30×10^{-4}
Benzene	2.36×10^{-3}	5.61×10^{-4}	1.99×10^{-3}
Bromochloromethane	1.64×10^{-3}	5.28×10^{-4}	1.70×10^{-3}
Bromodichloromethane	2.51×10^{-3}	8.06×10^{-4}	7.37×10^{-3}
Bromoform	1.98×10^{-3}	8.71×10^{-4}	1.23×10^{-2}
Carbon tetrachloride	7.79×10^{-4}	4.28×10^{-4}	1.10×10^{-3}
Chloroethane	5.74×10^{-4}	3.36×10^{-4}	7.19×10^{-4}
Chloroform	1.86×10^{-3}	6.53×10^{-4}	2.92×10^{-3}
Dibromochloromethane	3.18×10^{-3}	8.55×10^{-4}	1.09×10^{-2}
Dibromomethane	2.08×10^{-3}	7.45×10^{-4}	4.80×10^{-3}
Dichloromethane	1.59×10^{-3}	6.44×10^{-4}	2.79×10^{-3}
Ethylbenzene	1.35×10^{-3}	7.01×10^{-4}	4.06×10^{-3}
Ethylene	5.68×10^{-5}	4.11×10^{-5}	5.81×10^{-5}
Furan	1.93×10^{-3}	5.88×10^{-4}	2.16×10^{-3}
Halothane	2.17×10^{-4}	3.45×10^{-4}	7.58×10^{-4}
Hexachloroethane	8.09×10^{-4}	4.71×10^{-4}	1.47×10^{-3}
Heptane	8.11×10^{-4}	3.68×10^{-4}	8.31×10^{-4}
Hexane (n-)	5.90×10^{-4}	2.15×10^{-4}	3.80×10^{-4}
Isoprene	2.88×10^{-4}	1.43×10^{-4}	2.33×10^{-4}
Methyl chloride	4.04×10^{-4}	2.83×10^{-4}	5.51×10^{-4}
Octane	3.77×10^{-3}	4.60×10^{-4}	1.25×10^{-3}
Pentachloroethane	6.82×10^{-4}	6.91×10^{-4}	3.49×10^{-3}
Propylene	1.36×10^{-4}	9.48×10^{-5}	1.43×10^{-4}
Styrene	1.16×10^{-3}	7.34×10^{-4}	4.82×10^{-3}
Tetrachloroethylene	7.61×10^{-4}	6.23×10^{-4}	2.71×10^{-3}
Toluene	1.96×10^{-3}	6.32×10^{-4}	2.83×10^{-3}
Trichloroethylene	5.97×10^{-4}	5.81×10^{-4}	2.20×10^{-3}
Vinyl chloride	2.66×10^{-4}	2.09×10^{-4}	3.67×10^{-4}
Xylene (m-)	1.16×10^{-3}	7.10×10^{-4}	4.25×10^{-3}
Xylene (o-)	7.38×10^{-4}	6.96×10^{-4}	3.82×10^{-3}

[a]Obtained using PBPK model based on QPPR-derived P_{ba} and CL_h developed in this study.

[b]Obtained using PBPK model integrating the experimental data on P_{ba} (Abraham et al., 2005) and setting E (extraction ratio) to a value between 0 and 1.

Table 3. Reliability analysis for the proposed model as a function of the uncertainty analysis and sensitivity analysis with regard to the predicted 24-h area under the venous blood concentration versus time curve (AUC_{24}).

(a) Blood:air partition coefficient

P_{ba}		Sensitivity		
		High (SC >= 0.5)	Medium (0.2 ≤ SC <0.5)	Low (SC <0.2)
Uncertainty	High (1 PC in AD for P_{ba})	**1,3,5-Triglycidyl-s-triazinetrione; 2,4,5-T; Acrylamide; Aldrin; Chlordane; Chlorinated camphene; Chlorinated diphenyl oxide (o-); DDT; Diethanolamine; Disulfiram; Endosulfan; Formamide; Heptachlor; Hexachloronaphthalene; Hydrogenated terphenyls; Methoxychlor; Octachloronaphthalene; Oxybis(p,p'-); Pentachloronaphthalene; Rotenone; Strychnine.**	1,1,2,2-Tetrabromoethane; Ammonium perfluorooctanoate; Dibutyl phthalate; Dieldrin; Endrin; Heptachlor epoxide; Hexachlorobenzene; Hexachlorobutadiene; Iodoform; Lindane; Pentachlorophenol; Tetrachloronaphthalene.	Alachlor; Bromacil; Carbon tetrabromide; Diquat; Pentachloronitrobenzene; Sulfometuron methyl; Warfarin
	Medium (1 to 2 PC in AD for P_{ba})	1-Methylnaphthalene; 2-Ethylhexanoic acid; 2-Methoxyethanol; 2-Methylnaphthalene; 2,4-D; 3,5-Dinitro-o-toluamide; 4-Methoxyphenol; 5-Nitro-o-toluidine; Acetophenone; Adipic acid; Amitrole; Anisidine (o-); Anisidine (p-); Biphenyl; Butyl lactate (n-); Camphor; Carbonyl fluoride; Carbonyl sulfide; Catechol; Citral; Cyclonite; Diacetyl; Dichloroacetic acid; Diethylene glycol monobutyl ether; Dimethylformamide; Dinitro-o-cresol; Dinitrobenzene (m-); Dinitrotoluene; Diquat; Ethylenediamine; Glyoxal; Hydroquinone; Methyl silicate; Metribuzin; Naphthalene; Nitrobenzene; Nitrochlorobenzene (p-); Nitroglycerin; Nitrotoluene (m-); Nitrotoluene (o-); Nitrotoluene (p-); Paraquat; Phenol; Phenyl ether; Phenyl glycidyl ether; Phenylenediamine (m-); Phthalonitrile (o-); Pindone; Simazine; Tetramethyl succinonitrile; Toluidine (m-); Toluidine (o-); Toluidine (p-); Trichloronaphthalene; Vinyl-2-pyrrolidone (N-); Vinylcyclohexene dioxide.	(2-Methoxymethylethoxy)propanol; 2-Aminopyridine; 2,4,6-Trinitrotoluene; ANTU; Diglycidyl ether; Isopropylaniline (N-); Nicotine; Nitroaniline (p-); Picloram; Terephthalic acid.	4,4'-Methylene dianiline; Atrazine; Diethyl ketone; Dinitrobenzene; Dinitrobenzene (o-); Dinitrobenzene (p-); Diphenylamine; Nitrapyrin; Phenylenediamine (o-); Quinone; Tetranitromethane
	Low (3 PC in AD for P_{ba})	1-Bromopropane; 1-Butene; 1-Chloro-1-nitropropane; 1-Chloro-2-propanol; 1-Hexene; 1-Nitropropane; 1,1,1,2-Tetrachloro-2,2-difluoroethane; 1,1,2-Trichloro-1,2,2-trifluoroethane; 1,1,2,2-Tetrachloro-1,2-difluoroethane; 1,3-Dichloropropene; 1,3-Dioxolane; 2-Butene; 2-Butene (cis-); 2-Butene (trans-); 2-Butoxyethyl acetate; 2-Chloro-1-propanol; 2-Chloropropionic acid; 2-Ethoxyethanol; 2-Ethoxyethyl acetate; 2-Isopropoxyethanol; 2-Methylbutane; 2-Methylhexane; 2-Nitropropane; 2-Propanol; 2,2-Dimethylbutane; 2,2-Dimethylpentane; 2,3-Dimethylbutane; 2,3-Dimethylpentane; 2,4-Dimethylpentane; 2,4-Pentanedione; 3-Methylhexane; 3-Methylpentane; Acetone; Acrylonitrile; Allyl chloride; Amyl methyl ether (tert-); Aniline; Butanol (sec-); Butanol (tert-); Butene; Butyl glycidyl ether (n-); Carbon disulfide; Carbon monoxide; Chlorobenzene; Chlorodifluoromethane; Chloropicrin; Chlorostyrene (o-); Cumene; Cyclohexane; Cyclohexanol; Cyclopentane; Dichlorobenzene (o-); Dichlorobenzene (p-); Dichloroethyl ether; Dichlorofluoromethane; Dichlorotetrafluoroethane; Difluorodibromomethane; Diisopropylamine; Dimethyl disulfide; Dimethylaniline; Enflurane; Epichlorohydrin; Ethyl acrylate; Ethyl amyl ketone; Ethyl bromide; Ethyl butyl ketone; Ethyl ether; Ethyl mercaptan; Ethyl silicate; Ethyl tert-butyl ether; Ethylene glycol dinitrate; Ethyleneimine; Hexafluoroacetone; Hexafluoropropylene; Indene; Isobutene; Isopropyl acetate; Ketene; Mesityl oxide; Methanol; Methyl acetate; Methyl acethylene; Methyl acrylate; Methyl chloroform; Methyl cyclohexane; Methyl cyclohexanone (o-); Methyl ethyl ketone; Methyl formate; Methyl iodide; Methyl isoamyl ketone; Methyl isobutyl carbinol; Methyl isobutyl ketone; Methyl isopropyl ketone; Methyl mercaptan; Methyl methacrylate; Methyl n-butyl ketone; Methyl tert-butyl ether; Methylacrylonitrile; Methylal; Methylaniline (N-); Morpholine; Neopentane; Nitroethane; Nitromethane; Nonane; Pentane; Perfluorobutyl ethylene; Phenyl mercaptan; Propargyl alcohol; Propyl nitrate (n-); Propylene dichloride; Pyridine; Tetrafluoroethylene; Tetrahydrofuran; Trifluorobromomethane; Vinyl acetate; Vinylidene fluoride; Xylene (p).	1,2-dichloroethylene; 2-Diethylaminoethanol; 2-Methoxyethyl acetate; 4-Vinyl cyclohexene; Acetic acid; Butyl toluene (p-tert-); Dimethylacetamide (N, N-); Ethyl morpholine (N-); Isopropylamine; Propyleneimine.	(1-methylethenyl)-Benzene; 2-Oxetanone; Propylene glycol dinitrate; Triethylamine

AD, applicability domain; P_{ba}, blood:air partition coefficient; PC, physicochemical properties (*MW*, LogP_{ow}, or Log*VP*); SC, sensitivity coefficient. High reliability (clear); medium reliability (grey shading); low reliability (bold font).

(b) Hepatic clearance

CL_h		Sensitivity		
		High (SC >= 0.5)	Medium (0.2 ≥ SC <0.5)	Low (SC <0.2)
Uncertainty	High ($LogP_{ow} > 5$)	**Aldrin; Chlordane; Chlorinated camphene; Chlorinated diphenyl oxide (o-); DDT; Dieldrin; Endrin; Heptachlor; Hexachlorobenzene; Hexachloronaphthalene; Hydrogenated terphenyls; Methoxychlor; Octachloronaphthalene; Pentachloronaphthalene; Pentachloronitrobenzene; Tetrachloronaphthalene; Trichloronaphthalene.**	1,1,2-Trichloro-1,2,2-trifluoroethane; 2,3-Dimethylpentane; 2,4-Dimethylpentane; 3-Methylhexane; Cyclopentane; Methyl cyclohexane; Perfluorobutyl ethylene.	
	Medium ($2 \leq LogP_{ow} \leq 5$)	(1-methylethenyl)-Benzene; 1-Bromopropane; 1-Methylnaphthalene; 1,1,1,2-Tetrachloro-2,2-difluoroethane; 1,1,2,2-Tetrabromoethane; 1,1,2,2-Tetrachloro-1,2-difluoroethane; 1,3-Dichloropropene; 2-Ethylhexanoic acid; 2-Methylnaphthalene; 4-Vinyl cyclohexene; 4,4'-Methylene dianiline; Alachlor; Atrazine; Biphenyl; Butyl toluene (p-tert-); Camphor; Carbon tetrabromide; Chlorobenzene; Chlorostyrene (o-); Citral; Cumene; Cyclohexane; Dibutyl phthalate; Dichlorobenzene (o-); Dichlorobenzene (p-); Dimethylaniline; Dinitro-o-cresol; Diphenylamine; Diquat; Disulfiram; Endosulfan; Ethyl amyl ketone; Heptachlor epoxide; Hexachlorobutadiene; Indene; Iodoform; Isopropylaniline (N-); Lindane; Methyl chloroform; Naphthalene; Nitrapyrin; Nitrochlorobenzene (p-); Nitrotoluene (m-); Nitrotoluene (o-); Nitrotoluene (p-); Nonane; Pentachlorophenol; Phenyl ether; Phenyl mercaptan; Pindone; Rotenone; Xylene (p-).		1-Butene; 2-Butene; 2-Butene (cis-); 2-Butene (trans-); 2-Methylbutane; 2-Methylhexane; 2,2-Dimethylbutane; 2,2-Dimethylpentane; 2,3-Dimethylbutane; 2,4-D; 2,4,5-T; 3-Methylpentane; 5-Nitro-o-toluidine; ANTU; Butene; Dichlorotetrafluoroethane; Dinitrotoluene; Enflurane; Hexafluoropropylene; Isobutene; Neopentane; Pentane; Propylene dichloride; Simazine; Warfarin.
	Low ($LogP_{ow} < 2$)	(2-Methoxymethylethoxy)propanol; 1-Chloro-1-nitropropane; 1-Chloro-2-propanol; 1-Nitropropane; 1,2-dichloroethylene; 1,3-Dioxolane; 1,3,5-Triglycidyl-s-triazinetrione; 2-Aminopyridine; 2-Butoxyethyl acetate; 2-Chloro-1-propanol; 2-Chloropropionic acid; 2-Diethylaminoethanol; 2-Ethoxyethanol; 2-Ethoxyethyl acetate; 2-Isopropoxyethanol; 2-Methoxyethanol; 2-Methoxyethyl acetate; 2-Nitropropane; 2-Oxetanone; 2-Propanol; 2,4-Pentanedione; Acetic acid; Acetone; Acetophenone; Acrylonitrile; Amitrole; Ammonium perfluorooctanoate; Aniline; Anisidine (o-); Butanol (sec-); Butanol (tert-); Butyl glycidyl ether (n-); Butyl lactate (n-); Carbon monoxide; Cyclohexanol; Diacetyl;Dichloroethyl ether; Diethyl ketone; Diglycidyl ether; Diisopropylamine; Dimethyl disulfide; Dimethylacetamide (N,N-); Dimethylformamide; Epichlorohydrin; Ethyl acrylate; Ethyl butyl ketone; Ethyl morpholine (N-); Ethyl silicate; Ethylene glycol dinitrate; Ethylenediamine; Ethyleneimine; Glyoxal; Isopropyl acetate; Isopropylamine; Ketene; Mesityl oxide; Methanol; Methyl acetate; Methyl acrylate; Methyl cyclohexanone (o-); Methyl ethyl ketone; Methyl isoamyl ketone; Methyl isobutyl carbinol; Methyl isobutyl ketone; Methyl isopropyl ketone; Methyl n-butyl ketone; Methyl silicate; Methylacrylonitrile; Methylal; Methylaniline (N-); Morpholine; Nicotine; Nitrobenzene; Nitroethane; Nitroglycerin; Nitromethane; Paraquat; Phenol; Phenyl glycidyl ether; Picloram; Propargyl alcohol; Propylene glycol dinitrate; Propyleneimine; Pyridine; Quinone; Terephthalic acid; Tetrahydrofuran; Tetranitromethane; Toluidine (m-); Toluidine (o-); Toluidine (p-); Triethylamine; Vinylcyclohexene dioxide;	Acrylamide; Allyl chloride; Amyl methyl ether (tert-); Carbon disulfide; Catechol; Chloropicrin; Difluorodibromomethane; Ethyl bromide; Ethyl ether; Ethyl tert-butyl ether; Methyl formate; Methyl iodide; Methyl methacrylate; Methyl tert-butyl ether; Phthalonitrile (o-); Propyl nitrate (n-); Vinyl acetate.	2,4,6-Trinitrotoluene; 3,5-Dinitro-o-toluamide; 4-Methoxyphenol; Adipic acid; Anisidine (p-); Bromacil; Carbonyl fluoride; Carbonyl sulfide; Chlorodifluoromethane; Cyclonite; Dichloroacetic acid; Dichlorofluoromethane; Diethanolamine; Diethylene glycol monobutyl ether; Dinitrobenzene; Dinitrobenzene (m-); Dinitrobenzene (o-); Dinitrobenzene (p-); Diquat; Ethyl mercaptan; Formamide; Hexafluoroacetone; Hydroquinone; Methyl acethylene; Methyl mercaptan; Metribuzin; Nitroaniline (p-); Oxybis(p,p'-); Phenylenediamine (m-); Phenylenediamine (o-); Strychnine; Sulfometuron methyl; Tetrafluoroethylene; Tetramethyl succinonitrile; Trifluorobromomethane; Vinyl-2-pyrrolidone (N-); Vinylidene fluoride.

AD, applicability domain; CL_h, hepatic clearance; SC, sensitivity coefficient. High reliability (clear); medium reliability (grey shading); low reliability (bold font).

(c) Grouping of chemicals as per reliability categories

Chemicals						
1-Butene;	2-Methylbutane;	Butanol (sec-);	Dinitrobenzene;	Hexafluoropropylene;	Methyl isopropyl ketone;	Propyleneimine; Pyridine;
1-Chloro-1-nitropropane;	2-Methylhexane;	Butanol (tert-);	Dinitrobenzene (o-);	Isobutene;	Methyl mercaptan;	Quinone;
1-Chloro-2-propanol;	2-Nitropropane;	Butene;	Dinitrobenzene (p-);	Isopropyl acetate;	Methyl methacrylate;	Sulfometuron methyl;
1-Nitropropane;	2-Oxetanone;	Butyl glycidyl ether (n-);	Diquat;	Isopropylamine;	Methyl n-butyl ketone;	Tetrafluoroethylene;
1,2-dichloroethylene;	2-Propanol;	Carbon disulfide;	Enflurane;	Ketene;	Methyl tert-butyl ether;	Tetrahydrofuran;
1,3-Dioxolane;	2,2-Dimethylbutane;	Carbon monoxide;	Epichlorohydrin;	Mesityl oxide;	Methylacrylonitrile;	Tetranitromethane;
2-Butene;	2,2-Dimethylpentane;	Chlorodifluoromethane;	Ethyl acrylate;	Methanol;	Methylal;	Triethylamine;
2-Butene (cis-);	2,3-Dimethylbutane;	Chloropicrin;	Ethyl bromide;	Methyl acetate;	Methylaniline (N-);	Trifluorobromomethane;
2-Butene (trans-);	2,4-Pentanedione;	Cyclohexanol;	Ethyl butyl ketone;	Methyl acethylene;	Morpholine;	Vinyl acetate;
2-Butoxyethyl acetate;	3-Methylpentane;	Dichloroethyl ether;	Ethyl ether;	Methyl acrylate;	Neopentane;	Vinylidene fluoride;
2-Chloro-1-propanol;	Acetic acid;	Dichlorofluoromethane;	Ethyl mercaptan;	Methyl cyclohexanone (o-);	Nitroethane;	Wafarin.
2-Chloropropionic acid;	Acetone;	Dichlorotetrafluoroethane;	Ethyl morpholine (N-);	Methyl ethyl ketone;	Nitromethane;	
2-Diethylaminoethanol;	Acrylonitrile;	Diethyl ketone;	Ethyl silicate;	Methyl formate;	Pentane;	
2-Ethoxyethanol;	Allyl chloride;	Difluorodibromomethane;	Ethyl tert-butyl ether;	Methyl iodide;	Phenylenediamine (o-);	
2-Ethoxyethyl acetate;	Amyl methyl ether (tert-);	Diisopropylamine;	Ethylene glycol dinitrate;	Methyl isoamyl ketone;	Propargyl alcohol;	
2-Isopropoxyethanol;	Aniline;	Dimethyl disulfide;	Ethyleneimine;	Methyl isobutyl carbinol;	Propyl nitrate (n-);	
2-Methoxyethyl acetate;	Bromacil;	Dimethylacetamide (N, N-);	Hexafluoroacetone;	Methyl isobutyl ketone;	Propylene dichloride;	
					Propylene glycol dinitrate;	
1-Methylnaphthalene;	Biphenyl;	Dinitro-o-cresol;	Hexachlorobutadiene;	Lindane;	Nitrotoluene (m-);	Pentachlorophenol;
1,1,2,2-Tetrabromoethane;	Camphor, synthetic;	Diquat;	Iodoform;	Naphthalene;	Nitrotoluene (o-);	Phenyl ether, vapor;
2-Ethylhexanoic acid;	Citral;	Heptachlor epoxide;	Isopropylaniline (N-);	Nitrochlorobenzene (p-);	Nitrotoluene (p-);	Pindone.
2-Methylnaphthalene;	Dibutyl phthalate;					
Aldrin; Chlordane;	**Chlorinated camphene;**	**Chlorinated diphenyl oxide (o-);**	**DDT; Heptachlor;**	**Hexachloronaphthalene; Hydrogenated terphenyls;**	**Methoxychlor;**	**Octachloronaphthalene; Pentachloronaphthalene**

High reliability (clear; n = 115); medium reliability (grey shading; n = 23); low reliability (bold font; n= 11).

Chapitre 5. Derivation of internal dose-based thresholds of toxicological concern for occupational inhalation exposure to systemically acting organic chemicals

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Derivation of internal dose-based thresholds of toxicological concern for occupational inhalation exposure to systemically acting organic chemicals

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Abstract

This study aimed at deriving occupational thresholds of toxicological concern for inhalation exposure to systemically-acting organic chemicals using predicted internal doses. The latter were also used to evaluate the quantitative relationship between occupational exposure limit and internal dose. Three internal dose measures were identified for investigation: (i) the daily area under the venous blood concentration *vs.* time curve, (ii) the daily rate of the amount of parent chemical metabolized, and (iii) the maximum venous blood concentration at the end of an 8-hr work shift. A dataset of 276 organic chemicals with 8-hr threshold limit values- time-weighted average was compiled along with their molecular structure and Cramer classes (Class I: low toxicity, Class II: intermediate toxicity, Class III: suggestive of significant toxicity). Using a human physiologically-based pharmacokinetic model, the three identified dose metrics were predicted for an 8-hr occupational inhalation exposure to the threshold limit value for each chemical. Distributional analyses of the predicted dose metrics were performed to identify the percentile values corresponding to the occupational thresholds of toxicological concern. Also, simple linear regression analyses were performed to evaluate the relationship between the 8-hr threshold limit value and each of the predicted dose metrics, respectively. No threshold of toxicological concern could be derived for class II due to few chemicals. Based on the daily rate of the amount of parent chemical metabolized, the proposed internal dose-based occupational thresholds of toxicological concern were 5.61×10^{-2} and 9×10^{-4} mmol/d at the 10^{th} percentile level for classes I and III, respectively, while they were 4.55×10^{-1} and 8.50×10^{-3} mmol/d at the 25^{th} percentile level. Even though high and significant correlations were observed between the 8-hr threshold limit values and the predicted dose metrics, the one with the rate of the amount of chemical metabolized was remarkable regardless of the Cramer class (r^2 = 0.81; n = 276).

The proposed internal dose-based occupational thresholds of toxicological concern are potentially useful for screening-level assessments as well as prioritization within an integrated occupational risk assessment framework.

Key Words: Data-poor chemicals; occupational health risk assessment; PBPK modeling; quantitative property-property relationship; threshold of toxicological concern

5.1. Introduction

Health-based occupational exposure limits (OELs) are important tools for evaluating workers' health risk arising from inhalation of airborne chemicals in workplace settings. More specifically, health-based OELs can help guide the selection and application of appropriate hazard (and exposure) control measures.[1, 2] In this regard, the time-weighted average (TWA) threshold limit values (TLV®) of the American Conference of Governmental Industrial Hygienists (ACGIH®) have been used for developing some control and risk-based tools.[3, 4]

For data-rich chemicals, the development of health-based OELs can be based on human observations and/or experimental animal data on the type of hazard, and the point of departure (e.g., no-observed adverse effect level (NOAEL), benchmark dose) with application of uncertainty factors and duration adjustment factors.[5-9] For a large number of new and existing data-poor chemicals (including the emerging chemicals) which do not have adequate health hazard databases, the challenge is much greater.[10] In such cases, pragmatic exposure control tools and approaches available to the hygienists include the occupational exposure banding and the control banding.[11, 12] Another relevant tool to deal with chemicals that lack health effects data, is the one that has been used successfully for conducting screening level risk assessments in the food safety, pharmaceutical and cosmetics areas, i.e., the threshold of toxicological concern (TTC).[13-15]

The TTC refers to ingested doses or inhalation concentrations of chemicals that would not represent a safety concern. Initially for the oral route, this approach was implemented to place untested or new chemicals, on the basis of similarity to molecular features of chemicals with animal toxicity data, into one of three classes for which the TTCs have been established, specifically class I (chemicals exhibiting low order of toxicity such as those with simple

structures and innocuous metabolic products), class II (chemicals exhibiting intermediate toxicity), and class III (chemical structures and metabolites suggestive of significant toxicity and not supporting any strong presumption of safety). Extensive literature exists on the development, evaluation and application of oral and inhalation TTCs for various groups of chemicals and their usage sectors.[13-15] However, the development of TTC for occupational inhalation exposure to chemicals is still in the embryonic stage.[16]

Chebekoue and Krishnan[16] developed TTCs for each of the three Cramer classes, based on absorbed dose resulting from inhalation exposure to systemically-acting organic chemical vapors at the 8-hr TLV-TWA level.[17] The occupational TTCs proposed by Chebekoue and Krishnan [16] are based on human data (i.e., TLV-TWAs and bioavailability) and expressed in terms of mmol/day, while all the other existing TTCs are based on animal data (e.g., rodent NOAEL) and expressed in terms of mg/m^3 or mg/day.[18,19]

For the occupational inhalation exposures, it would be scientifically sound to develop TTCs on the basis of absorbed dose or other measures of internal dose. Even though the use of absorbed dose (i.e., the fraction of inhaled dose that crosses the alveolar membrane to enter systemic circulation) represents one level of refinement of TTCs, it is preferable to enhance the basis of TTC development by basing it on measures of internal dose that are better reflective of systemic exposure to toxic chemicals and are more closely related (than the absorbed dose) to the onset of systemic toxicity. Such measures of internal dose are: (i) the area under the blood concentration *vs.* time curve during a work shift (AUC); (ii) the maximum blood concentration at the end of an 8-hr work shift (CMAX); and (iii) the amount of parent chemical metabolized during a specified period of time (RMET). Despite the tremendous interest in developing internal dose-based TTCs, there has not been much progress in this regard.[19] However, TTCs

based on internal dose metrics would provide a scientifically-sound basis for evaluations. Besides, the relationship between internal dose and OEL has not been extensively explored. Few studies have developed pharmacokinetic modeling approaches to support the derivation of internal dose-based OELs for pharmaceutical substances [20] or other organic chemicals.[21-24] In this regard, physiologically-based pharmacokinetic (PBPK) models have been used to both predict the internal dose and reduce the uncertainties (e.g., inter-species differences and inter-individual variability) inherent to the OEL derivation process.[21-23] One of the major impediments to making progress in the application of PBPK models in OEL or TTC derivation is the inability to predict metabolism rates of chemicals from their molecular structure information. Therefore, it is currently of interest to the research and regulatory communities to develop novel approaches to predict metabolism rates to develop rapidly human PBPK models for new and emerging chemicals. Most recently, such a PBPK modeling approach has been implemented for more than 200 workplace contaminants to generate predictions of internal dose associated with the inhalation route of exposure (Chebekoue and Krishnan[24] and references therein).

The use of PBPK models, by enabling the prediction of internal dose in workers associated with the OELs of a variety of chemicals, can help advance the state of knowledge regarding the differences in toxicity potencies and TTCs among occupational contaminants. This has not been investigated thus far. Therefore, the aim of the current study was to derive occupational thresholds of toxicological concern (OTTCs) for inhalation exposure to systemically-acting organic chemicals on the basis of PBPK model predictions of internal doses (i.e., AUC, CMAX, and RMET). The PBPK model simulations of AUC, CMAX and RMET obtained in this study were also used to inform on the quantitative relationship between occupational exposure limit (i.e., 8-hr TLV-TWAs) and the internal dose metrics.

5.2. Methods

For this study, the 8-hr TLV-TWA values for systemically-acting organic chemicals (in the form of gases and vapors and not aerosols) published by the ACGIH in 2016 were chosen as the sole source of OEL data [16, 17] since they are widely known and applied health-based values. Thus, using a human quantitative property-property relationship (QPPR)-PBPK model,[24] a dataset of internal doses was compiled using chemical structure information for an 8-hr inhalation exposure to the TLV-TWAs (see Supplemental material). Thereafter, distributional analyses of the dose metrics were performed to derive the OTTCs. Finally, the quantitative relationships between the resulting predictions of internal doses and 8-hr TLV-TWA were investigated.

5.2.1. Dataset compilation

5.2.1.1. Data Sources

A dataset of 276 systemically-acting organic chemicals with available 8-hr TLV-TWA values [16, 17] along with the chemical-specific data on physicochemical properties, specifically Log P_{ow}, molecular weight (MW), air:water partition coefficient (P_{aw}) and vapor pressure (VP), and first-order elimination rate constant (K_{el}) were obtained from Chebekoue and Krishnan. [24] The substances (n=276) used in the current study represent the entirety of the database of Chebekoue and Krishnan.[24] In the latter study, for the purpose of expanding the application domain of the model, 27 substances used in the initial validation exercise were removed and thus the PBPK model was applied to the remaining 249 substances. However, the current study applied the same PBPK model framework to all 276 chemicals, without necessitating the creation or treatment of subset of chemicals, as in the previous study. Each of these chemicals was assigned to one of three Cramer structural classes using the software program Toxtree, version 2.6.13, as per Chebekoue and Krishnan.[16] Accordingly, the substances belonging to the Cramer class I were considered to be of low order of toxicity, possessing simple structures and amenable to efficient metabolism to innocuous products; class II substances are less innocuous than those belonging to class I but without indication of potential toxicity that characterizes clss III substances; and class III chemicals possess structural features that do not support

presumption of innocuity or absence of risk to worker health, or are amenable for metabolism to potentially toxic reactive products. For each chemical in the dataset, the predictions of internal dose following an inhalation exposure (i.e., 8-hr per workday exposure to TLV-TWA followed by a period of 16-hr no-exposure) were obtained using a human QPPR-PBPK model, as described in the following section.

5.2.1.2. PBPK modeling

A human PBPK model, based on integration of QPPRs for organic chemicals, was obtained from Chebekoue and Krishnan[24] and parameterized to reflect worker physiology. This model depicted human body as a set of four perfusion-limited tissue compartments (liver, adipose tissue, muscle plus skin, and reminder of the body) interconnected by the systemic circulation and the gas-exchange lungs to describe chemical uptake by the inhalation route (Figure 1). This PBPK model accounted for chemical metabolism in liver and elimination via lungs (i.e., exhalation), but not the renal excretion of unchanged parent chemical or the toxicokinetics of metabolites formed in the liver. Of the input parameters required for the PBPK model,

(i) the physiological data for an adult worker were obtained from Tardif et al. [25] since they account for the increase in pulmonary ventilation and blood flow to muscles during working conditions (Table 1);

(ii) the tissue:air partition coefficients (P_{ta}) were computed from chemical structure and tissue (lipid and water) composition as per Poulin and Krishnan [26];

(iii) the blood:air partition coefficients (P_{ba}) were calculated based on *MW*, *VP* and *Log* P_{ow} [27]; and

(iv) the hepatic clearances were obtained from Chebekoue and Krishnan[24] on the basis of K_{el} values from the PK explorer module of the ACD/Labs Percepta software, version 14.0.0 (Advanced Chemistry Development, Toronto, ON, Canada).

For each chemical in the dataset, the PBPK model was used to predict three measures of internal dose using the following scenario: inhalation exposure to 8-hr TLV-TWA for 8 hr while performing a light physical activity (50 W) followed by a 16-hr rest (no chemical exposure). The predicted internal dose metrics were:

(i) the area under the venous blood concentration vs. time curve during 24 hr (AUC_{24}),

(ii) the rate of the amount of parent chemical metabolized during the day ($RMET_{24}$), and

(iii) the maximum venous blood concentration at the end of an 8-hr workshift ($CMAX_8$).

All the PBPK simulations were performed with MATLAB software (The MathWorks, Inc., Natick, MA) and the mass balance differential equations were solved by numerical integration using the Matlab solver *ode15s*.

A dataset of model outputs for the 276 systemically-acting organic chemicals was compiled in SPSS for Windows (Version 25, SPSS, Chicago, IL) for further analysis.

5.2.2. Data Analysis

For the current analyses, the OEL, namely the 8-hr TLV-TWA, was identified as the response variable whereas the internal dose metrics and the physicochemical properties were considered as the predictor variables. To study the relationship between the OEL and the internal

dose, all analyses were first performed on the entire dataset, then separately for each Cramer class: I (low toxicity), II (intermediate toxicity) and III (high toxicity). Also, the 5^{th}, 10^{th} and 25^{th} percentiles of the internal dose distribution for each Cramer class-based subset were identified to develop OTTC values.

Bivariate correlation analyses were performed to identify any significant linear relationships between the variables, with primary focus on measures of internal dose (i.e., $AUC_{24,}$ $RMET_{24,}$ $CMAX_8$). If there were any, these relationships were quantified using the Pearson correlation coefficient (r). Also, only the internal dose and the physicochemical properties not estimated from other variables in these analyses were accounted for. Once the predictor variables with the highest correlations towards the 8-hr TLV-TWA identified, simple linear regressions were performed for modeling the relationship between the internal dose and OEL.

The data preparation and the statistical analyses were performed with the SPSS software and the significance was set at $p < 0.05$.

5.3. Results

5.3.1. Descriptive Statistics

Figure 2 presents the PBPK model simulation of the venous blood vs. time curve for four of the contaminants in the dataset. The simulated data on internal dose measures ($AUC_{24,}$ $RMET_{24,}$ $CMAX_8$) for each of the 276 chemicals in the dataset are provided in the Supplemental material. Table 2 presents the descriptive statistics of all the variables used in the current study. The mean values of 8-hr TLV-TWA, Log P_{aw}, Log VP and all the three dose metrics were highly variable and decreased from class I (less toxic) to class III (most toxic); however, no clear trend was observed for MW and K_{el}. Whereas the AUC_{24} ranged from 4.55×10^{-9} to 48.89 mmol/L.hr for the entire set of chemicals, the $CMAX_8$ ranged from 2.28×10^{-8} to 6.12 mmol/L and the

$RMET_{24}$ values ranged from 7.09×10^{-6} to 86.27 mmol/d. The PBPK model simulated mean values of AUC_{24} (mmol/L.hr) were 1.00 ± 5.48, 0.52 ± 0.58 and 0.09 ± 0.37, respectively, for Cramer Classes I, II and III. Similarly, the PBPK model simulated mean values of $RMET_{24}$ (mmol/d) were 6.57 ± 12.51, 3.66 ± 4.78 and 1.46 ± 9.92, respectively for Cramer Classes I, II and III. For the dose metric of $CMAX_8$, the mean values obtained with PBPK modeling were 0.12 ± 0.68, 0.05 ± 0.06 and 0.009 ± 0.03, respectively, for Cramer Classes I, II and III.

5.3.2. Distributional Analysis

Figure 3 displays the cumulative probability distributions of the internal dose metrics of occupational contaminants modeled in this study. Table 3 shows the calculated parametric percentiles (5^{th}, 10^{th}, 25^{th}, 50^{th} and 95^{th}) from the empirical cumulative density function of the internal dose metrics from each Cramer class. No uncertainty or adjustment factors were applied to these calculated internal dose metrics as they were directly derived from the 8-hr TLV-TWA values for worker. The OTTC values based on combined distributions of values for classes II and III were similar to the individual class values obtained for class III (data not shown). Moreover, given that there were only 11 chemicals in class II, all further analyses were conducted for Cramer class I (n=82) and Class III (n=183) chemicals only. Accordingly, the 5^{th}, 10^{th} and 25^{th} percentiles of each Cramer class are proposed as internal dose-based OTTCs. For Cramer classes I and III, the metabolism-based OTTCs derived in this study corresponded to 0.015 and 0.0004 mmol/worker/day at the 5^{th} percentile level, while the values were 0.056 and 0.0009 mmol/worker/day at the 10^{th} percentile level. Comparable level of difference existed in the $RMET_{24}$ dose metric between classes I and III at the 25^{th} percentile level (0.46 and 0.0085 mmol/worker/day, respectively). Similarly, the AUC_{24}-based OTTCs derived in this study corresponded to 0.0002 and 0.00001 mmol/L.hr at the 5^{th} percentile level for Cramer classes I and III, respectively; whereas the values were 0.001 and 0.000006 mmol/L.hr at the 10^{th} percentile level. Somewhat lower magnitude of difference between classes I and III was seen at the 25^{th} percentile level (0.026 and 0.00035 mmol/L.hr, respectively). Regarding $CMAX_8$, the 5^{th} percentile values for Cramer classes I and III corresponded to 1.8×10^{-5} mmol/L and 5.6×10^{-8} mmol/L, whereas the 10^{th} percentile values were 9.1×10^{-5} mmol/L and 5.1×10^{-7} mmol/L, respectively. The 25^{th} percentile values of $CMAX_8$ differed by a factor of 80 between the two Cramer classes (2.6×10^{-3} vs. 3.3×10^{-5} mmol/L) (Table 3).

5.3.3. Correlation Analysis

The evaluation of the correlations between the 8-hr TLV-TWA and the internal dose metrics yielded results that were all less than optimal ($r < 0.5$) (data not shown). Given the spread of the data, further analyses were performed following logarithmic transformation of the data. For the entire dataset, the results of this analysis showed high and significant positive correlations between the Log 8-hr TLV-TWA and the Log internal dose-metrics, with the highest correlation being observed between Log 8-hr TLV-TWA and the Log transformed rate of metabolism simulated with PBPK models ($r = 0.90$; $p < 0.01$). This was followed by Log VP ($r = 0.7$; $p < 0.01$) as well as MW ($r = -0.61$; $p < 0.01$) and Henry's law constant ($r = 0.56$; $p < 0.01$) (Table 4). The same trends were consistently observed among the Cramer classes. Besides the internal dose metrics, other high and significant positive associations were observed between Log 8-hr TLV-TWA and Log P_{aw} for class I compounds ($r = 0.68$; $p < 0.01$), and between Log 8-hr TLV-TWA and Log VP for class III compounds ($r = 0.7$; $p < 0.01$) (Table 4).

5.3.4. Quantitative relationships between internal dose and OEL

The results from these analyses indicated that all internal dose metrics were strong predictors of the TLV based on the entire dataset or by Cramer class. The quantitative relationships between internal dose metrics and 8-hr TLV-TWA are shown in Figure 4. Using all data, the following regression equations were obtained to describe the quantitative relationship between the OEL and internal dose simulated using PBPK models:

$$\text{Log}\,(\text{TLV, ppm}) = 1.13 + 0.98 \times \text{Log}\,(\text{RMET}_{24}, \text{mmol/d}) \quad (1)$$

$$\text{Log}\,(\text{TLV, ppm}) = 1.88 + 0.71 \times \text{Log}\,(\text{AUC}_{24}, \text{mmol/L.hr}) \quad (2)$$

$$\text{Log}\,(\text{TLV, ppm}) = 2.51 + 0.68 \times \text{Log}\,(\text{CMAX}_{8}, \text{mmol/L}) \quad (3)$$

5.4. Discussion

Health-based OELs are important reference values useful for the quantitative risk assessment and health risk characterization in exposed workers.[4,5,8,17] However, several

chemicals that might occur in workplace settings still do not have a designated health-based OEL due to the lack of toxicity data relevant to occupational exposures. One of the tools relevant for use in such a situation is the threshold of toxicological concern (TTC), based on historical and scientific experience in areas of food and cosmetic safety assessment over the past four decades.

Chebekoue and Krishnan,[16] for the first time, extended this concept to develop the occupational TTC (OTTCs), on the basis of absorbed dose in workers for 289 chemicals in the TLV database. However, for systemically-acting chemicals, the internal dose (i.e., AUC, RMET, CMAX) is a more reliable index of toxicity than the exposure concentration or absorbed dose [20, 22]. Thus, the present work further extends the OTTC concept to identify thresholds of internal dose of toxicological concern, based on simulations with PBPK models. The study is unique as it jointly applied risk assessment tools such as the molecular structure-based Cramer classification and QPPR-PBPK models to 276 systemically-acting organic chemicals, along with the database of 8-hr TLV-TWAs. From the three internal dose-metrics predicted with PBPK models (i.e., AUC_{24}, $RMET_{24}$ and $CMAX_{8}$), probability distributions were developed to identify internal dose-based OTTCs, for the first time.

The use of a human QPPR-PBPK modeling framework allowed the prediction of internal dose for a large number of occupational contaminants primarily from the sole use of their physicochemical properties (i.e., Log P_{ow}, P_{aw}, molecular weight and vapor pressure). Furthermore, by integrating QPPR derived-chemical-specific pharmacokinetic parameters (e.g., K_{el}, V_d), this modeling framework enabled the consideration of the variability in the internal dose among the chemicals in the analyses. This modeling approach, covering the same application domain and level of confidence as reported by Chebekoue and Krishnan,[24] was

implemented for 276 chemicals. The integrated QPPR-PBPK model along with the reliability assessment (as reported by Chebekoue and Krishnan [24]) allowed the prediction of internal doses of chemicals belonging to diverse chemical classes with different molecular structures, in contrast to individual QPPRs that have limited application domains (e.g., application domain of a QPPR for metabolism rate: $0.16 \leq \text{Log } P_{blood:water} \leq 2.49$; $1.09 \leq \text{Log } P_{ow} \leq 4.03$; $9.13 \leq$ ionization potential ≤ 11.28).[24] For 60% of the chemicals in the database, the PBPK model simulations of internal doses are moderately to highly reliable, as reported by Chebekoue and Krishnan.[24] Since the experimental measures of internal doses associated with the worker exposure to TLV-TWA level are not available for all chemicals, the PBPK modeling approach used in the current study with attendant uncertainty serves the purpose of lower tier approaches in risk assessment (e.g., OTTCs). This is remarkable considering the number of data-poor and emerging chemicals which lack relevant pharmacokinetic data to allow scientifically-sound assessments. In addition, the categorization of chemicals as per their Cramer class represents an added-value in facilitating screening level assessments using OTTCs for data-poor chemicals in the workplace.

In addition to developing thresholds of internal dose, the current study also investigated the quantitative relationship between the molecular structure-based internal dose and the OEL, for application to data-poor chemicals using linear regression analyses. Indeed, statistically significant associations between internal dose and 8-hr TLV-TWAs were uncovered in this study. Thus, the analyses conducted indicate that a measure of internal dose, namely the amount of chemical metabolized daily ($RMET_{24}$), can be used as a reasonable predictor variable of the 8-hr TLV-TWA. Strong relationships between OELs and the effective internal concentration of occupational toxicants ($r^2 = 0.787$) [28] or the maximum blood concentration of drugs (i.e.,

quinidine) and OEL [20] have been previously reported using steady-state algorithms or one-compartment pharmacokinetic modeling, respectively. Even though the internal dose was deemed a strong predictor of the OEL, the results of the current analyses did not support the use and development of regression models specific to each Cramer class to predict the OEL. Moreover, the current study, in accordance with previous studies, indicated a significant difference between Cramer classes I and III; and that the results from merging chemicals from Cramer classes II and III together were not significantly different from those obtained with Cramer class III alone.

The current study yielded OTTC values, for example, of 0.056 and 0.0009 mmol/worker/day at the 10^{th} percentile level for classes I and III, respectively, based on rate of metabolism of chemicals. Using PBPK models, these rates of metabolism can be converted to parent chemical doses or concentrations, for the inhalation route or for any other route. Choosing two chemicals yielding the exact levels of internal dose of TTC for worker exposure to the TLV-TWA (i.e., 0.056 and 0.0009 mmol/worker/day for sulfometuron methyl and hexachloronaphthalene, respectively), the back-calculation using PBPK model would yield occupational inhalation exposure concentrations of 5 mg/m^3 and 0.2 mg/m^3, respectively. In comparison, Chebekoue and Krishnan,[16] using the TLV database and absorption fraction, derived 10^{th} percentile values of 0.82 and 0.04 mg/m^3 for systemically-acting organic chemicals belonging to Cramer classes I and III. On the contrary, for these two Cramer classes, approaches not accounting for the toxicokinetics or bioavailability (ECETOC,[29] in line with Munro et al.[18] and Kroes et al.[30]) would yield inhalation TTCs of 1.8 and 0.1 mg/m^3 for workers (assuming a breathing rate of 10 m^3/day).

The present study successfully integrated molecular structure- and property-based approaches with worker physiology using PBPK models to provide rapid predictions of internal dose. The database of internal dose metrics (i.e., AUC_{24}, $RMET_{24}$, $CMAX_8$) generated for a large number of organic chemicals in this study is the first of its kind, that would not only facilitate the implementation of scientifically-sound TTCs but also the interpretation of biomarker data collected in workers (e.g., $CMAX_8$).

The TTCs are generally considered to be a pragmatic tool for screening-level assessment and prioritization, particularly applicable for chemicals lacking OELs or health effect data required to develop such guidance values. Thus, as pointed out by Chebekoue and Krishnan,[16] the appropriate manner for using the OTTCs is to compare them with worker exposure levels associated with proposed or actual uses of the given chemical. When the estimated exposure level is well below the OTTC for the structural class to which the chemical belongs, then there is no justifiable indication of a high priority for immediate safety testing or resource-intensive evaluation. However, when the predicted or measured internal dose in workers is higher than the OTTC benchmark for a given Cramer class, then it points to focused evaluation of exposure and/or chemical-specific health effects. For the occupational contaminants, the OTTC benchmarks based on internal dose (i.e., AUC_{24}, $RMET_{24}$, $CMAX_8$) were developed for the 5^{th}, 10^{th}, or 25^{th} percentiles in this study. If the worker exposure (or dose) yields internal doses that are below the chosen percentile value (e.g., 10^{th} or 25^{th} percentile) for that particular internal dose metric, then it will indicate low priority to conduct more detailed testing to generate compound-specific data for that particular chemical relative to other candidate chemicals which may need to be tested. Pragmatically, in choosing the appropriate percentile of the OTTC to screen out a specific chemical, risk management considerations should focus on the type of

worker population, context of chemical use, as well as purpose of screening evaluation and implementation.

5.5. Conclusion

The internal dose-based thresholds of toxicological concern proposed in the current study are potentially useful tools for screening-level risk assessment and prioritization of data-poor or untested chemicals that might occur in workplace settings. The present study has demonstrated the pragmatic usefulness of state-of-the-art approaches such as the integrated QPPR-PBPK modeling and the Cramer classification in the development of OTTC values. The approach proposed is unique as it both accounts for inter-chemical variability in internal dose and toxicological potential in generalizing results from studied to unstudied chemicals, based on their molecular structure information. As database on OELs improve and results from high-throughput toxicity tests emerge, the proposed internal dose-based OTTCs for workers can be further refined to ensure protection of worker health in the sphere of uncertainty when newer chemicals are used to enhance productivity and innovative applications.

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5.7. Funding

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5.9. Figures

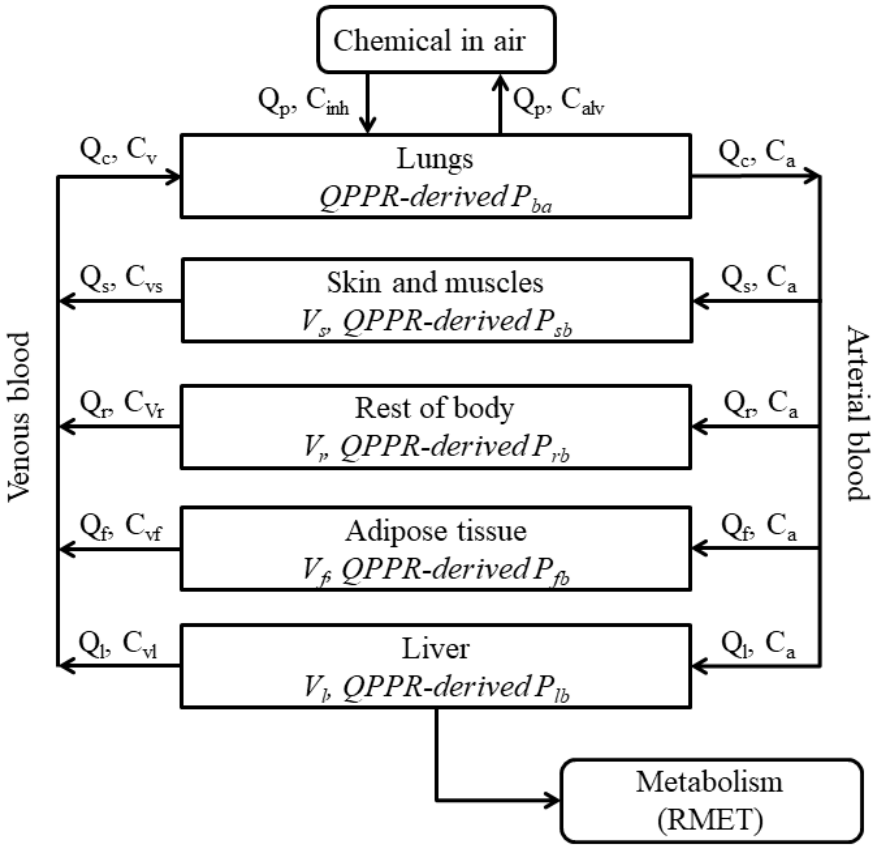


Figure 1. Human physiologically based pharmacokinetic model.

C_a = arterial concentration; C_{alv} = alveolar concentration; C_{inh} = inhaled concentration; C_V = venous blood concentration; C_{vt} = concentration in venous blood leaving the corresponding tissue t (f, adipose tissue; l, liver; r, rest of body; s, skin and muscles); P_{ba} = blood:air partition coefficient; P_{tb} = tissue:blood partition coefficient for tissue t; Q_p = alveolar ventilation; Q_c = cardiac output; Q_t = blood flow rate of the corresponding tissue t; RMET = rate of amount metabolized; V_t = volume of the corresponding tissue t.

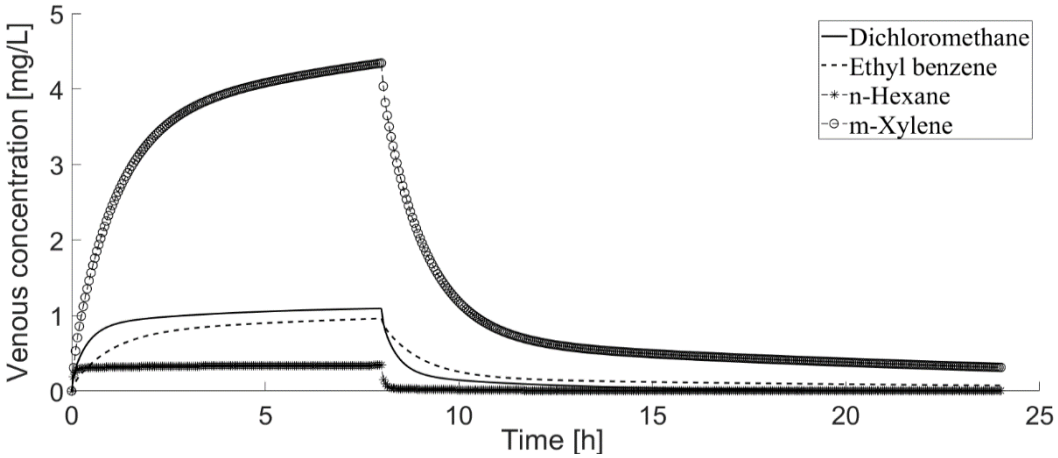
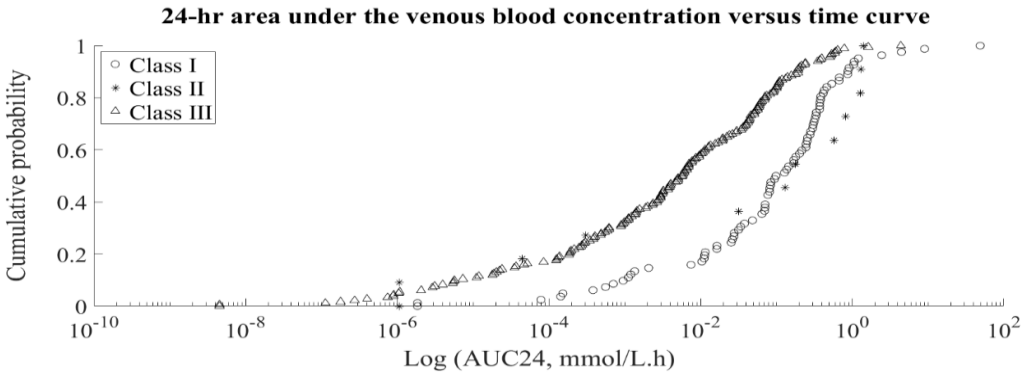


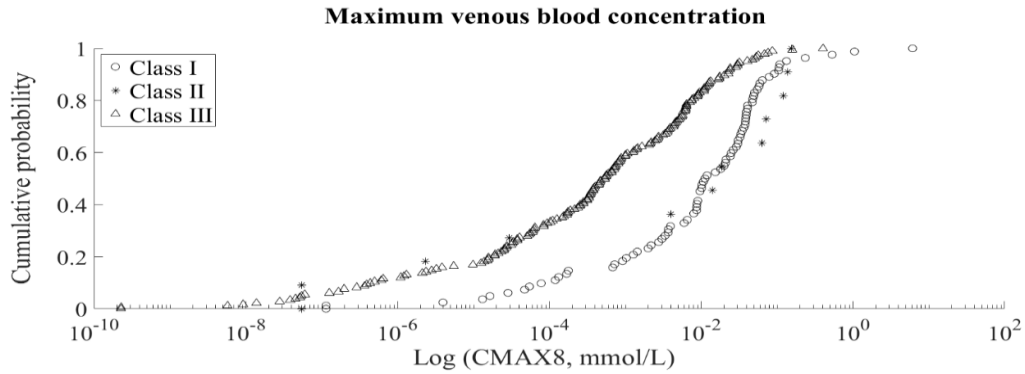
Figure 2. PBPK model simulations of the venous blood concentration-time curves following an 8-hr worker exposure to the threshold limit value- time-weighted average of four chemicals in the dataset

(dichloromethane, 50 ppm; ethyl benzene, 20 ppm; n-hexane, 50 ppm; m-xylene, 100 ppm).

a.



b.



c.

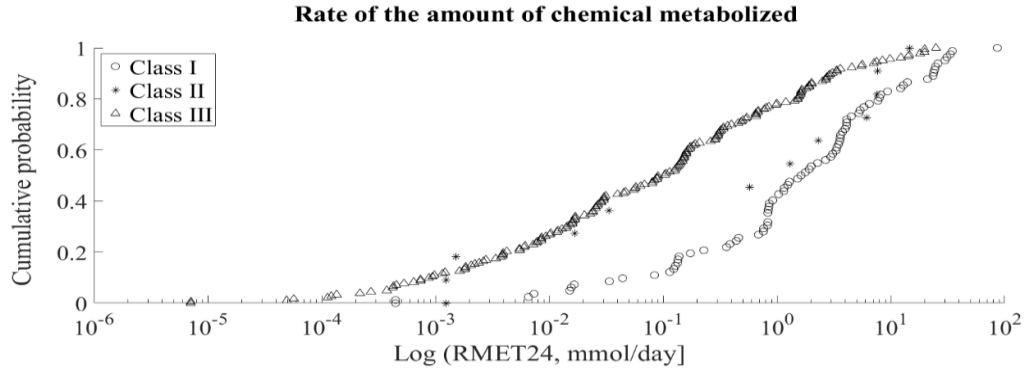
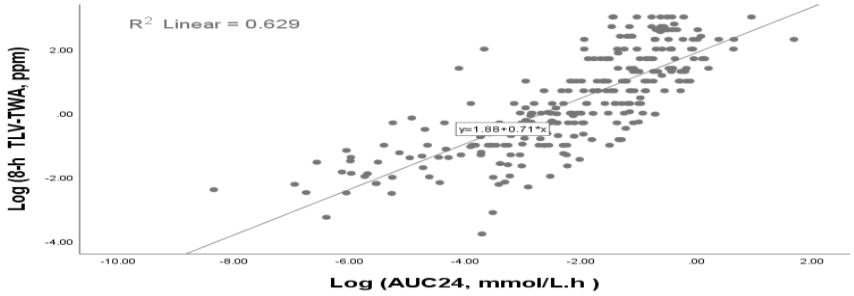


Figure 3. Cumulative density function of the simulated internal dose metrics (AUC_{24}, $CMAX_8$, $RMET_{24}$) for the occupational contaminants belonging to Cramer classes I, II and III.

(a) AUC_{24}, 24-hr area under the venous blood concentration vs. time curve; (b) $CMAX_8$, maximum venous blood concentration at the end of an 8-hr work shift; (c) $RMET_{24}$, rate of the amount of parent chemical metabolized during 24 hr.

a.



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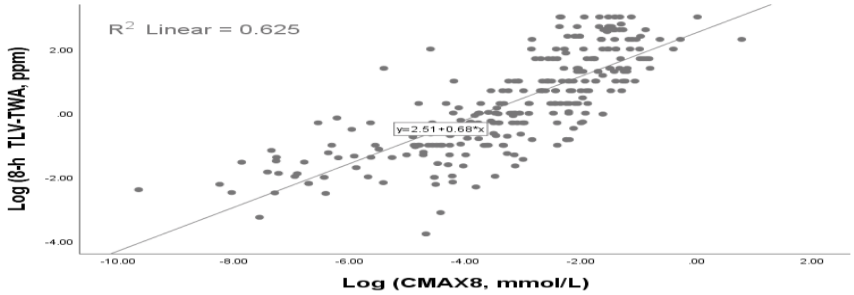

c.

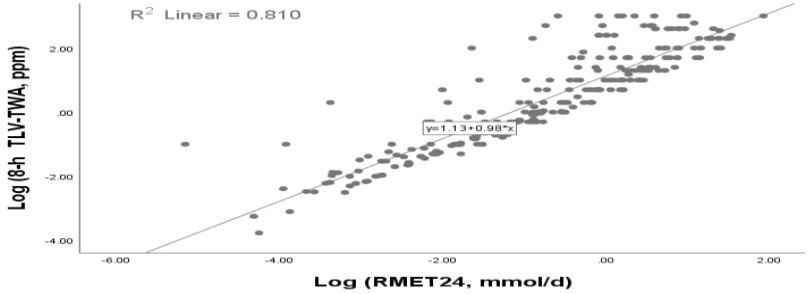

Figure 4. Quantitative relationship between the predicted internal dose metrics (AUC_{24}, $CMAX_8$, $RMET_{24}$) and TLV-TWA of workplace chemicals investigated in the current study.

(a) AUC_{24}, 24-hr area under the venous blood concentration versus time curve; (b) $CMAX_8$, maximum venous blood concentration at the end of an 8-hr work shift; (c) $RMET_{24}$, rate of the amount of parent chemical metabolized during 24 hr.

5.10. Tables

Table 1. Human physiological parameter values used in the generic QPPR-based PBPK model for data-poor organic chemicals.

Parameter	Value
Body weight (kg)*	70
Flow rates at rest*	
Cardiac output ($L/h/Kg^{0.7}$)*	18
Alveolar ventilation ($L/h/Kg^{0.7}$)*	18
Blood flow rates as a fraction of cardiac output*	
Adipose tissue	0.05
Skin and muscles	0.25
Rest of body	0.44
Liver	0.26
Flow rates at 50 W*	
Cardiac output ($L/h/Kg^{0.7}$)*	30.8
Alveolar ventilation ($L/h/Kg^{0.7}$)*	67.6
Blood flow rates as a fraction of cardiac output*	
Adipose tissue	0.06
Skin and muscles	0.51
Rest of body	0.27
Liver	0.16
Tissue volume as a fraction of body weight*	
Adipose tissue	0.19
Skin and muscles	0.734
Rest of body	0.05
Liver	0.026
Neutral lipid equivalents as a fraction of tissue volume (F_{nle})†	
Adipose tissue	0.7986
Skin and muscles	0.0378
Liver and Rest of body	0.0473
Water equivalents as a fraction of tissue volume (F_{we})†	
Adipose tissue	0.1514
Skin and muscles	0.7573
Liver and Rest of body	0.7400

*Obtained from Tardif et al.[25]

†Obtained from Poulin and Krishnan.[26]

Table 2. Summary of the descriptive statistics of the variables used in the study.

	Log 8-hr TLV-TWA (ppm)	MW (g/mol)	Log P_{ow}	Log P_{aw}	Log VP	K_{el} (min^{-1})	AUC_{24} (mmol/L.hr)	$RMET_{24}$ (mmol/d)	$CMAX_8$ (mmol/L)
					Entire (n = 276)				
Mean	0.4	146.47	1.91	-2.67	1.75	2.16×10^{-3}	0.38	3.06	0.04
SD	1.50	89.05	1.82	3.29	3.19	1.18×10^{-3}	3.02	7.91	0.38
Variance	2.26	7930.67	3.32	10.81	10.19	1.00×10^{-6}	9.13	62.52	0.141
Median	0.30	114.19	1.68	-2.24	2.67	2.00×10^{-3}	0.02	0.29	0.002
Min	-3.77	28.01	-2.82	-18.06	-9.05	3.30×10^{-4}	4.55×10^{-9}	7.09×10^{-6}	2.28×10^{-10}
Max	3.00	431.10	8.55	3.89	6.62	9.10×10^{-3}	48.98	86.27	6.12
					Class I (n= 82)				
Mean	1.45	95.87	1.84	-1.39	3.27	2.30×10^{-3}	1.00 ± 5.48	6.57	0.12
SD	1.16	39.31	1.42	2.30	2.03	9.86×10^{-4}	5.48	12.51	0.68
Variance	1.35	1545.05	2.03	8.97	4.11	9.72×10^{-7}	30.05	156.50	0.47
Median	1.70	96.13	1.68	-1.15	3.83	2.00×10^{-3}	0.11	1.70	0.01
Min	-1.97	28.01	-0.91	-9.67	-2.80	1.10×10^{-3}	1.85×10^{-6}	4.46×10^{-4}	1.14×10^{-7}
Max	3.00	278.35	4.76	2.44	6.62	8.30×10^{-3}	48.98	86.27	6.12
					Class II (n = 11)				
Mean	0.49	113.08	1.50	-2.25	2.53	0.002	0.52	3.66	0.05
SD	1.42	49.19	2.65	2.00	1.57	0.0008	0.58	4.78	0.06
Variance	2.02	2.42×10^{3}	7.04	3.99	2.48	6.41×10^{-7}	0.34	22.84	3.58×10^{-3}
Median	1.00	108.10	1.54	-2.08	2.89	2.30×10^{-3}	0.18	1.30	0.02
Min	-2.00	58.04	-1.66	-6.46	-1.00	1.10×10^{-3}	1.07×10^{-6}	1.24×10^{-3}	5.50×10^{-8}
Max	2.00	248.46	8.55	2.02	4.58	4.40×10^{-3}	1.41	14.67	0.15
					Class III (n = 183)				
Mean	-0.08	171.16	1.96	-3.27	1.01	2.08×10^{-3}	0.09	1.46	9.19×10^{-3}
SD	1.40	96.59	1.93	3.32	3.44	1.27×10^{-3}	0.37	3.92	3.43×10^{-2}
Variance	1.97	9.33×10^{-3}	3.71	11.02	11.80	2.00×10^{-6}	0.13	15.40	1.18×10^{-3}
Median	-0.02	142.20	1.74	-2.76	1.62	2.00×10^{-3}	5.80×10^{-3}	0.10	5.42×10^{-4}
Min	-3.77	40.07	-2.82	-18.06	-9.05	3.30×10^{-4}	4.55×10^{-9}	7.09×10^{-6}	2.28×10^{-10}
Max	3.00	431.10	8.33	3.89	6.40	9.10×10^{-3}	4.41	24.97	0.40

AUC_{24} = 24-hr area under the venous blood concentration versus time curve; $CMAX_8$ = maximum venous blood concentration at the end of an 8-hr work shift; K_{el} = first-order elimination rate constant; Max = maximum; Min = minimum; MW = molecular weight; P_{aw} = air:water partition coefficient; P_{ow} = *n*-octanol:water partition coefficient; $RMET_{24}$ = rate of the amount of parent chemical metabolized during 24 hours; SD = standard deviation; TLV-TWA = 8-hr threshold limit value-time weighted average; VP = vapor pressure.

Table 3. Parametric percentiles of the predicted three internal dose metrics for occupational exposure to the systemically-acting chemicals belonging to Cramer classes I and III.

Percentile	AUC_{24} (mmol/L.hr)	$RMET_{24}$ (mmol/d)	$CMAX_8$ (mmol/L)
	Class I (n = 82)		
P_5	1.88×10^{-4}	1.52×10^{-2}	1.83×10^{-5}
P_{10}	1.01×10^{-3}	5.61×10^{-2}	9.10×10^{-5}
P_{25}	2.62×10^{-2}	4.55×10^{-1}	2.62×10^{-3}
P_{50}	1.14×10^{-1}	1.70×10^{0}	1.16×10^{-2}
P_{95}	2.27×10^{0}	30.92×10^{0}	0.22×10^{0}
	Class III (n = 183)		
P_5	1.05×10^{-6}	3.83×10^{-4}	5.55×10^{-8}
P_{10}	6.36×10^{-6}	9.00×10^{-4}	4.60×10^{-7}
P_{25}	3.47×10^{-4}	8.50×10^{-3}	3.26×10^{-5}
P_{50}	5.80×10^{-3}	0.10×10^{0}	5.42×10^{-4}
P_{95}	0.48×10^{0}	9.57×10^{0}	4.60×10^{-2}

AUC_{24} = 24-hr area under the venous blood concentration versus time curve; $CMAX_8$ = maximum venous blood concentration at the end of an 8-hr work shift; P = percentile; $RMET_{24}$ = rate of the amount of parent chemical metabolized during 24 hr.

Table 4. Pearson coefficients associated with the bivariate correlation analyses.

Variable	Log 8-hr TLV-TWA	MW	Log P_{ow}	Log P_{aw}	Log VP	Log AUC_{24}	Log $RMET_{24}$	Log $CMAX_8$
				Entire (n = 276)				
Log 8-hr TLV-TWA	1.00	-0.61**	-0.10	0.56**	0.70**	0.79**	0.90**	0.79**
MW	-0.61**	1.00	0.57**	-0.32**	-0.76**	-0.63**	-0.58**	-0.63**
Log P_{ow}	-0.10	0.57**	1.00	0.35**	-0.30**	-0.31**	-0.14*	-0.31**
Log P_{aw}	0.56**	-0.32**	0.35**	1.00	0.71**	0.38**	0.39**	0.40**
Log VP	0.70**	-0.76**	-0.30**	0.71**	1.00	0.51**	0.55**	0.52**
Log AUC_{24}	0.79**	-0.63**	-0.31**	0.38**	0.51**	1.00	0.87**	1.00**
Log $RMET_{24}$	0.90**	-0.58**	-0.14*	0.39**	0.55**	0.87**	1.00	0.86**
Log $CMAX_8$	0.79**	-0.63**	-0.31**	0.40**	0.52**	1.00**	0.86**	1.00
				Class I (n = 82)				
Log 8-hr TLV-TWA	1.00	-0.49**	0.27*	0.68**	0.62**	0.76**	0.81**	0.77**
MW	-0.49**	1.00	0.33**	-0.41**	-0.80**	-0.32**	-0.28*	0.33**
Log P_{ow}	0.27*	0.33**	1.00	0.61**	0.02	-0.02	0.13	0.004
Log P_{aw}	0.68**	-0.41**	0.61**	1.00	0.75**	0.40**	0.39**	0.43**
Log VP	0.62**	-0.80**	0.02	0.75**	1.00	0.32**	0.33**	0.35**
Log AUC_{24}	0.76**	-0.32**	-0.02	0.40**	0.32**	1.00	0.87**	1.00**
Log $RMET_{24}$	0.81**	-0.28*	0.13	0.39**	0.33**	0.87**	1.00	0.86**
Log $CMAX_8$	0.77**	-0.33**	0.004	0.43**	0.35**	1.00**	0.86**	1.00
				Class II (n = 11)				
Log 8-hr TLV-TWA	1.00	0.003	0.24	0.11	0.004	0.84**	0.99**	0.82**
MW	0.003	1.00	0.96**	0.89**	-0.85**	-0.15	-0.01	-0.16
Log P_{ow}	0.24	0.96**	1.00	0.85**	-0.81**	-0.002	0.22	-0.02
Log P_{aw}	0.11	0.89**	0.85**	1.00	-0.84**	0.16	0.15	0.16
Log VP	-0.04	-0.85**	-0.81**	-0.84**	1.00	0.002	-0.02	0.01
Log AUC_{24}	0.84**	-0.15	-0.002	0.16	0.002	1.00	0.90**	1.00**
Log $RMET_{24}$	0.99**	-0.01	0.22	0.15	-0.02	0.90**	1.00	0.88**
Log $CMAX_8$	0.82**	-0.16	-0.02	0.16	0.01	1.00**	0.88**	1.00
				Class III (n = 183)				
Log 8-hr TLV-TWA	1.00	-0.57**	-0.23**	0.47**	0.70**	0.75**	0.89**	0.75**
MW	-0.57**	1.00	0.65**	-0.24**	-0.73**	-0.63**	-0.55**	-0.63**
Log P_{ow}	-0.23**	0.65**	1.00	0.29**	-0.36**	-0.42**	-0.23**	-0.42**
Log P_{aw}	0.47**	-0.24**	0.29**	1.00	0.70**	0.31**	0.32**	0.32**
Log VP	0.70**	-0.73**	-0.36**	0.70**	1.00	0.48**	0.54**	0.49**
Log AUC_{24}	0.75**	-0.63**	-0.42**	0.31**	0.48**	1.00	0.84**	1.00**
Log $RMET_{24}$	0.89**	-0.55**	-0.23**	0.32**	0.54**	0.84**	1.00	0.83**
Log $CMAX_8$	0.75**	-0.63**	-0.42**	0.32**	0.49**	1.00**	0.83**	1.00

AUC_{24} = 24-hr area under the venous blood concentration versus time curve (mmol/L.hr); $CMAX_8$ = maximum venous blood concentration at the end of an 8-hr work shift (mmol/L); MW = molecular weight (g/mol); P_{aw} = air:water partition coefficient (unitless); P_{ow} = *n*-octanol:water partition coefficient (unitless); $RMET_{24}$ = rate of the amount of parent chemical metabolized during 24 hr (mmol/d); TLV-TWA = threshold limit value-time weighted average; VP = vapor pressure.

**Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

Chapitre 6. Discussion générale

Les valeurs limites d'exposition professionnelle (VLEP) constituent des outils pratiques de santé publique qui sont utilisés pour protéger la santé des travailleurs et pour caractériser et gérer les risques sanitaires qu'ils pourraient encourir du fait de leur exposition aux substances chimiques inhalables retrouvées dans l'air ambiant de leurs lieux de travail. Dans la réalité cependant, plusieurs substances chimiques ne possèdent pas de VLEP. Cette situation, longtemps décriée dans la littérature scientifique (et qui continue de l'être d'ailleurs), est due au manque de données de toxicité adéquates pour les substances d'intérêt. Bien que plusieurs approches conceptuelles aient été développées et proposées comme solutions de rechange, celles-ci sont majoritairement qualitatives. Le but de la recherche exécutée dans le cadre de la présente thèse était donc de développer des outils et des modèles quantitatifs pouvant permettre la caractérisation des risques sanitaires associés aux substances chimiques organiques sans VLEP, en utilisant la structure moléculaire et la dose interne.

Cette recherche a permis de développer des seuils de préoccupation toxicologique pour l'exposition professionnelle (OTTC – *Occupational Threshold of Toxicological Concern*) et des modèles prédictifs de valeurs limites provisoires pour l'exposition professionnelle aux substances chimiques organiques. Ainsi, dans les paragraphes qui suivent, nous présentons un exposé des contributions majeures de la recherche effectuée, suivi de quelques-unes de ses limites majeures.

6.1. Contributions majeures du projet de recherche

La recherche réalisée dans le cadre de cette thèse a contribué à l'avancement des connaissances en plusieurs points.

Comme le sous-entend la règle des 3R (réduction, raffinement, remplacement) en éthique de la recherche scientifique, le paradigme actuel de la toxicologie est à la réduction de l'utilisation des animaux expérimentaux pour obtenir des données scientifiques (p. ex. en réalisant des tests de toxicité). Dans cet esprit donc, l'approche basée sur le concept du seuil de préoccupation toxicologique (TTC - *Threshold of Toxicological Concern*) se veut une aide. Ainsi, en utilisant principalement l'information sur la structure moléculaire des substances, l'application de l'approche permettrait de 'filtrer' celles possédant des données d'exposition (mesurées ou prédites) et de ne prioriser que celles potentiellement plus préoccupantes d'un

point de vue sanitaire. Une telle approche permettrait en bout de ligne d'optimiser le temps, l'allocation et l'utilisation des ressources (financières et d'expertise) aux fins d'évaluations et de tests de toxicité (Kroes et al., 2004).

Lors de la première parution de l'article publié, il s'agissait, à notre connaissance, de la première fois que l'approche basée sur le concept du TTC était utilisée comme outil pour proposer des seuils provisoires pour l'exposition professionnelle dans le cadre de l'analyse du risque en SST. En effet, les OTTC proposés peuvent très bien être considérés dans la construction de cadres d'analyse comme celui proposé pour la hiérarchie des VLEP, à l'exemple de l'arbre de décision de Kroes et al. (2004). Cela devra cependant se faire en tenant compte du profil d'exposition des travailleurs (c.-à-d. données de mesures d'exposition, tâches exécutées). De plus, les OTTC représentent des outils possédant un potentiel scientifique solide pour l'évaluation de l'exposition professionnelle aux substances sans VLEP du fait de leur nature probabiliste (Waters et al., 2015).

Bien que mentionné plusieurs fois dans la littérature scientifique comme un outil pratique d'analyse du risque préliminaire qui serait très utile pour la gestion des risques sanitaires potentiels qui pourraient résulter de l'exposition aux substances n'ayant pas de VLEP (Deveau et al., 2015; ECETOC, 2006; Hennes, 2012; Maier, 2011), l'approche n'avait jusqu'alors fait que l'objet d'une étude exploratoire par un comité d'experts du centre européen d'écotoxicologie et de toxicologie (ECETOC – *European Centre for Ecotoxicology and Toxicology of Chemicals*) (ECETOC, 2006). Ainsi, en utilisant un nombre restreint de substances chimiques, l'ECETOC a proposé, pour les classes de Cramer I, II, et III respectivement, des TTC de 0,18 mg/m^3, 0,054 mg/m^3 et 0,009 mg/m^3 dans un 1er scénario et de 18 mg/m^3, 5,4 mg/m^3 et 0,9 mg/m^3 dans un 2^e scénario. Ces scénarios variaient selon que l'agence ait considéré un facteur d'incertitude composite de 100 ou aucun facteur d'incertitude. Ainsi, comme discuté dans le premier article de cette thèse, les choix des facteurs d'incertitude de l'ECETOC étaient dans un cas comme dans l'autre discutable dans un contexte d'exposition professionnelle. Récemment, Hoersch et al. (2018) ont aussi utilisé l'approche pour proposer un seuil de 50 µg/m^3 en utilisant des valeurs prescriptives (DNEL – *Derived No Effect Level*), sans discrimination selon la classe de Cramer. Or, l'avantage des OTTC proposés est qu'en plus d'être appliquée à un jeu de données aussi large (n = 279), l'approche a permis de prédire des seuils d'exposition en considérant le potentiel toxique des substances qui, lui, était prédit à partir

de la structure moléculaire des substances (c.-à-d. la classe structurelle de Cramer). Il s'agissait en fait de la première fois que des contaminants de l'air des lieux de travail étaient catégorisés selon la classification de Cramer et al. (1978).

De façon notoire, une contribution majeure de l'approche proposée est qu'elle utilise des valeurs d'exposition humaine directement applicable à la population d'intérêt (c.-à-d. les travailleurs), contrairement aux autres approches qui se basent sur les données d'expérimentations animales (p. ex. NO(A)EL (ECETOC, 2006) ou DNEL - applicable à l'exposition de la population générale à toute substance qui entre en circulation (Hoersch et al., 2018)) et qu'elle utilise des facteurs d'incertitude pour les variabilités inter-espèces et inter-individuelle. En effet, des facteurs d'incertitude importants sont généralement utilisés pour établir des valeurs limites d'exposition provisoires pour des substances ne possédant pas de VLEP, afin de compenser les lacunes des bases de données de celles-ci (Deveau et al., 2015).

Par ailleurs, le fait d'utiliser des POD, calculés à partir d'études expérimentales chez les animaux (Kroes et al., 2000; Kroes et al., 2004; Munro, Ford, Kennepohl et Sprenger, 1996) pour estimer les expositions humaines sans tenir compte de la biodisponibilité des substances (à la fois chez les animaux expérimentaux et les humains) a longtemps été décrié. Dans le même ordre d'idées, soulignons que les TTC traditionnels sont basés sur les doses externes d'exposition. Or, la dose interne d'exposition (ou tout simplement dose interne) est reconnue comme étant le meilleur indicateur de toxicité. De ce fait, le débat actuel dans la littérature scientifique porte sur le développement de TTC basés sur la dose interne (Adler et al., 2011; Hartung, 2017; Nielsen et Larsen, 2011; Partosch et al., 2015). Ainsi, la présente recherche est allée plus loin en raffinant la prédiction de l'exposition et en développant des OTTC basés sur la dose interne d'exposition.

Partosch et al. (2015) furent en fait les premiers à proposer des TTC basés sur la dose interne, cela en considérant la biodisponibilité des substances. Cependant, comme discuté longuement au chapitre 3, ces auteurs ont appliqué un algorithme (P_{ba}) destiné à l'humain à des données d'exposition animales, remettant en question la validité scientifique de leur proposition. En effet, il a été démontré que la liaison aux protéines plasmatiques, qui sous-tend le coefficient de partage sang:air est différente entre les rongeurs et l'humain (Béliveau, Lipscomb, Tardif et Krishnan, 2005; Buist, Wit-Bos, Bouwman et Vaes, 2012). Alors, contrairement à Partosch et al. (2015), nous avons utilisé un algorithme spécifique à l'espèce humaine (Buist et al., 2012).

Il s'agissait en fait de la première fois qu'un P_{ba} spécifique à l'humain était utilisé pour tenir compte de la variabilité de la biodisponibilité des substances pour prédire des TTC en utilisant l'information sur leur structure moléculaire, c.-à-d., leurs propriétés physico-chimiques.

Contrairement aux applications de l'approche du TTC précédentes pour l'inhalation (Carthew, Clapp et Gutsell, 2009; Drew, 2010; Drew et Frangos, 2007; Escher et al., 2010; Grant, Kadlubar, Erraguntla et Honeycutt, 2007), que ce soit dans notre cas (Chebekoue et Krishnan, 2017) ou dans celui de Partosch et al. (2015), la biodisponibilité par voie respiratoire de chaque substance dans la base de données fut considérée par le biais de son propre P_{ba}. Bien que ces études constituent des avancée majeures, seule la dose absorbée fut considérée du fait du P_{ba}, sans considération des autres caractéristiques toxicocinétiques des substances, telles que leur métabolisme ou leur distribution dans les tissus en fonction de leurs propriétés physico-chimiques et des caractéristiques des tissus. C'est alors que l'approche a été raffinée au chapitre 5 en utilisant le cadre structuré pour la modélisation intégrée QPPR-PBPK proposé au chapitre 4. Il s'agissait en fait de la première fois que la modélisation PBPK était intégrée dans un cadre (d'analyse) TTC dans le but de prédire des valeurs limites provisoires pour l'exposition professionnelle. L'utilisation de la modélisation PBPK (dose interne d'exposition) n'avait jusqu'alors été utilisée que pour réduire les facteurs d'incertitude (p. ex. la composante toxicocinétique du facteur d'incertitude pour l'extrapolation inter-espèce, la variabilité interindividuelle, l'extrapolation voie-voie).

Cette approche constitue une contribution majeure dans l'avancement des connaissances. En effet, bien que l'approche TTC soit indiquée pour les substances n'ayant pas de données, le développement de cet outil, qui se base sur les similarités structurelles des substances n'ayant pas de données avec celles qui en possèdent, nécessite au moins la connaissance de leurs propriétés physico-chimiques. De plus, non seulement l'approche TTC basée sur la dose interne permet les extrapolations (donc de réduire les FI), elle permet aussi de considérer la variabilité toxicocinétique et le métabolisme des substances dans la distribution des doses internes.

Il est cependant important de souligner que les OTTC proposés n'ont pas pour but de remplacer les VLEP déjà établies. Au contraire, dans des situations où les données de toxicité manquent, ils peuvent être utilisés, de pair avec les valeurs d'exposition (mesurées ou estimées chez les travailleurs pendant qu'ils exécutent leurs tâches ordinaires), comme instruments de

priorisation (ou d'évaluation préliminaire) intégrés dans une stratégie globale d'évaluation de l'exposition aux contaminants organiques (peu ou pas étudiés) de l'air. Dans tous les cas, la meilleure approche serait de les considérer comme composantes des premières étapes de la stratégie (p. ex. du bas de la pyramide conceptualisant la hiérarchie des VLEP, mentionnée au chapitre d'introduction de la thèse).

Une autre contribution majeure de la recherche effectuée a été d'explorer la relation quantitative qui existe entre la dose interne d'exposition et la VLEP. Debia et Krishnan (2010) l'ont fait plus tôt; mais limités par le manque de données, notamment sur le métabolisme, ces auteurs ont utilisé un simple algorithme basé sur les concepts de concentration à l'état d'équilibre pour prédire ce qu'ils ont appelé une dose interne effective, laquelle était significativement corrélée avec les données de VLEP-8h de l'ACGIH. Cependant, dans la recherche courante, l'utilisation de la modélisation PBPK a non seulement permis de prédire des doses internes, mais aussi celles de substances n'ayant pas de données sur leurs paramètres pharmacocinétiques, en utilisant l'information sur leur structure moléculaire, c.-à-d. leurs propriétés physico-chimiques. Tout comme Debia et Krishnan (2010), nous avons observé des corrélations fortes et significatives entre la dose interne et la VLEP. Mieux, les analyses de cette recherche étaient basées sur un échantillon plus grand de substances (n= 276 contre 16). De plus, en raffinant la mesure de l'exposition, la recherche nous a permis de faire des analyses plus détaillées en identifiant les mesures de dose interne les plus significativement corrélées à la VLEP. Il s'agit d'une avancée majeure, car depuis les travaux de Debia et Krishnan (2010), déjà révolutionnaires à l'époque, peu sinon pas de recherche n'a été effectuée sur le sujet. Cependant, l'évaluation de la possibilité d'utiliser les modèles prédictifs développés aux fins de prédictions et de généralisations ont démontré que ces fins seraient prématurées compte tenu du contexte de notre recherche. En effet, du fait des erreurs de prédictions associées à la modélisation QPPR-PBPK et aux régressions, cette approche serait difficilement défendable pour les dites fins. Ces résultats indiquent toutefois que la relation quantitative entre la dose interne d'exposition et la VLEP mérite d'être étudiée par des analyses plus poussées que celles que nous avons effectuées, par exemple, en utilisant des régressions multivariées logistiques ou non linéaires. D'autant plus que ce type d'analyses pourrait permettre de raffiner les calculs d'autres instruments utilisés pour évaluer et pour caractériser le potentiel dangereux des substances en SST (p. ex. rapport de danger des vapeurs (VHR - *vapor hazard ratio*).

Parlant du cadre structuré pour la modélisation pharmacocinétique à haut débit en utilisant la structure chimique des substances proposé au chapitre 4, il se veut un outil pour permettre les évaluations préliminaires des substances n'ayant pas de données exhaustives. En effet, malgré l'utilité des modèles PBPK pour l'analyse du risque, la construction de ces derniers est parfois limitée, voire impossible, pour les substances dont les données sur leurs paramètres pharmacocinétiques sont inconnues (p. ex. volume de distribution, constante d'élimination). Alors, plusieurs efforts ont été déployés pour prédire ces paramètres pharmacocinétiques (Kirman et al., 2015; Peyret et Krishnan, 2012; Poulin et Krishnan, 1996). Cependant, les domaines d'application sont généralement limités, particulièrement pour ce qui est du métabolisme. Or, dans un objectif d'évaluation préliminaire du risque, la précision des estimés ne devrait pas être la priorité; ce sont plutôt la plage de valeurs et l'impact des incertitudes des valeurs prédites des paramètres sur celles de la variable d'intérêt, dans ce cas la dose interne, qui devraient être priorisés. Ainsi, au lieu de toujours développer des modèles prédictifs de paramètres pharmacocinétiques, la recherche développée au chapitre 4 s'est penchée sur l'intégration de quelques algorithmes publiés et ayant des domaines d'application large (Buist et al., 2012; Poulin et Krishnan, 1996) et elle s'est concentrée sur l'analyse de fiabilité des valeurs prédites de la dose interne. La validation de l'approche est d'autant plus pertinente qu'elle s'est basée sur un nombre considérable de substances (n = 276) provenant d'une même source. Aussi, il s'agissait de la première fois que l'on intègre des volumes de distribution prédits qui tiennent compte des caractéristiques des compartiments tissulaires du modèle (Vt, composition en eau et en lipides).

Le métabolisme a longtemps été et continue d'être un paramètre difficile à prédire. L'utilisation de la structure moléculaire a permis de prédire la constante d'élimination (de 1er ordre; K_{el}) à partir des approches QSAR (Bois et al., 2017) empruntant des concepts au domaine pharmaceutique. Compte tenu du fait que le K_{el} était prédit à partir d'un modèle unicompartimental, sa combinaison au volume de distribution prédit dans un modèle PBPK a permis de prédire des valeurs pour le métabolisme des substances afin d'obtenir des évaluations préliminaires. Il s'agit ici d'une première, car un modèle PBPK est conceptuellement multi-compartimental. En intégrant ainsi des paramètres toxicocinétiques tous prédits à partir de la structure moléculaire, l'approche proposée a permis, dans une continuité des recherches

précédentes, d'élargir les domaines d'applications des modèles QSAR-PBPK existants (Béliveau et al., 2005; Peyret et Krishnan, 2012). Il s'agit là d'une avancée majeure car les efforts précédents ayant utilisé le taux d'élimination s'étaient limités à des modèles unicompartimentaux (Bois et al., 2017).

De plus, l'utilisation du cadre de modélisation QPPR-PBPK pour les estimations à haut débit a permis : i) les prédictions de la dose interne d'un nombre considérable de substances organiques, et ii) de considérer la variabilité toxicocinétique des substances, et donc de leurs doses internes, dans les analyses. Tout cela en intégrant les paramètres pharmacocinétiques (p. ex. taux d'élimination, volume de distribution) dépendant de la structure chimique, et prédits à partir des QPPR. Cela s'est fait en utilisant principalement les propriétés physico-chimiques des substances (c.-à-d. les coefficients de partage *n*-octanol:eau, la constante de la loi de Henry, le poids moléculaire et la pression de vapeur). Ceci est particulièrement attrayant lorsqu'on a affaire aux substances existantes, émergentes ou nouvelles, qui sont peu étudiées et, par conséquent, pour lesquelles il n'y a pratiquement pas de données de toxicité, donc pas de VLEP.

Par conséquent, le cadre de modélisation proposé pourrait très bien être utilisé dans un contexte réglementaire à l'exemple du « Plan de gestion des produits chimiques (PGPC) » au Canada (mieux connu sous la dénomination : *Chemical Management Plan – CMP*). Soulignons que l'approche basée sur le TTC est utilisée dans le cadre du PGPC pour prioriser les substances. Cependant, que ce soit pour la plupart des évaluations préliminaires ou pour l'application du TTC dans le cadre du PGPC, ces évaluations se basent sur des considérations structurelles, sans tenir compte des paramètres pharmacocinétiques/toxicocinétiques (p. ex. volume de distribution, constante d'élimination) des substances, car ceux-ci sont généralement inexistants pour les substances peu ou pas étudiées.

6.2. Limites principales de la recherche effectuée

Malgré ses contributions, la recherche a connu quelques limites qui méritent d'être discutées. Tout d'abord, la base de données des VLEP utilisées comprenait des gaz, des vapeurs et des aérosols qui n'ont pas été séparés lors des analyses. La seule opération effectuée a été la conversion de ppm (gaz et vapeurs) à mg/m^3 (aérosols) et vice versa, selon le type de l'analyse à effectuer. Il est pourtant bien connu que les propriétés physico-chimiques des aérosols

affecteraient leur comportement pharmacocinétique/toxicocinétique, avec comme possible conséquence d'influencer les prédictions de leurs doses internes. En effet, en plus de leurs propriétés physico-chimiques (p. ex., masse moléculaire, solubilité et pression de vapeur considérées dans cette recherche), la taille des particules constituant un aérosol (solide ou liquide) et plus spécifiquement leurs diamètres aérodynamiques, est un paramètre très important qui influence leur absorption. Ainsi, comme illustré par les courbes de dépôt (p. ex., le modèle du « *Task Group on Lung Dynamics* »), le dépôt spatial (ou régional) des fractions gravimétriques d'un aérosol (dans les divers compartiments anatomiques du système respiratoire) dépend de la distribution du diamètre aérodynamique de celles-ci (Austin, 2004). Or, dans nos analyses, bien que la fraction respirable (c.à.d. celle qui atteint les alvéoles ou le poumon profond, région où a lieu les échanges gazeux) des dits aérosols ait été considérée la plupart du temps, il existe des cas où les fractions *IFV* (pour « *Inhalable Fraction and Vapor* », correspondant à celle dans laquelle une substance peut coexister dans ses phases particulaire et gazeuse, selon l'ACGIH) ou inhalables (c.à.d. celles dont les particules peuvent se déposer n'importe où dans le tractus respiratoire) ont été considérées. Nous avons donc supposé que toutes les substances étudiées atteignent les alvéoles et sont absorbées en fonction de leurs propriétés physico-chimiques et selon leur coefficient de partage sang:air. Dans le cas des substances contenues dans les fractions *IFV* (p. ex., acrylamide, alachlor, aldrin, azinphos-methyl, dieldrin, diéthanolamine, endosulfan) et inhalables (p. ex., 2,4-D, diquat, warfarin, simazine, p,p'-Oxybis(benzenesulfonyl hydrazide), 3,5-Nitro-o-toluidine), ceci aurait théoriquement pour conséquence de sous-estimer ou surestimer la dose interne prédite. Par ailleurs, soulignons que tout ceci ne pourrait invalider les résultats de la recherche car son ampleur anticipée ne saurait être grande compte tenu des incertitudes associées aux hypothèses de recherche émises, celles associées aux QPPR et de la nature probabiliste de l'approche TTC. Tous ces points ont d'ailleurs été discutés dans les chapitres 3 à 5. Dans un souci d'avancement des connaissances, il serait intéressant d'explorer l'impact de l'isolation des aérosols dans les analyses futures comme ce fut le cas en catégorisant les substances selon la classe de Cramer.

Par ailleurs, en plus de la classification de Cramer, il aurait fallu ségréguer la base de données selon l'effet toxicologique pour tenir compte autant que possible du mode d'action différent des substances. En effet, bien que les cancérogènes, les sensibilisants et les irritants

non pas été considérées dans l'approche TTC, les reprotoxiques eux ont été inclus, pourtant de plus en plus, on note une spécificité dans les analyses par rapport à ces agents chimiques (Hoersch et al., 2018).

Aussi, bien que l'approche TTC ait été validée jusqu'ici seulement pour les substances avec toxicité chronique, il aurait tout de même été intéressant d'explorer l'irritation. Notre analyse s'est pourtant limitée à considérer seulement les effets systémiques et chroniques. En effet, plusieurs efforts ont commencé à explorer l'application de l'approche à l'irritation (Carthew et al., 2009; Escher et al., 2010).

Une autre limite est le fait que les prédictions de plusieurs variables aient été basées sur des valeurs moyennes. Bien que les limites du métabolisme aient été considérées pour la construction du modèle PBPK du chapitre 4, il aurait été souhaitable de tenir compte de la variabilité des autres paramètres du modèle en utilisant des distributions ou des plages de valeurs des variables considérées (p. ex. variabilité du métabolisme). Cela aurait pu se faire, par exemple, à l'aide des simulations Monte Carlo.

Finalement, il aurait été intéressant d'étudier la contribution de l'exposition cutanée à la charge corporelle totale. Bien que les VLEP s'appliquent seulement à l'inhalation, en réalité, il est possible qu'une certaine exposition cutanée survienne, due par exemple à l'hygiène des travailleurs ou à l'utilisation des produits. Ainsi, avec le cadre de modélisation proposé dans cette thèse (voir chapitre 4), qui peut très bien être ajusté pour tenir compte des voies d'exposition autres que l'inhalation, il serait intéressant, dans des analyses futures, d'étudier la contribution de l'exposition cutanée à la dose interne. Cela serait d'autant plus pertinent que bon nombre de substances de la base de données constituée dans le cadre de cette thèse possédaient la mention « peau » qui, selon l'ACGIH, indique que la contribution de l'exposition cutanée à la charge corporelle totale de ces substances serait significative.

Conclusion générale

Les valeurs limites d'exposition professionnelles représentent des instruments essentiels qui ont fait leur preuve dans le cadre de la protection des travailleurs, de la caractérisation et de la gestion des risques sanitaires associés aux substances pouvant se retrouver dans l'air ambiant des milieux de travail. Malgré la remise en question perpétuelle et les critiques à l'égard de leur efficience réelle, ces valeurs de référence demeurent des instruments tangibles en santé et en sécurité au travail. Cependant, plusieurs substances n'ont toujours pas de VLEP établies. Or, l'approche basée sur le concept du seuil de préoccupation toxicologique (TTC – *Threshold of Toxicological Concern*) a une longue histoire dans le domaine de la sécurité des aliments, et de plus en plus dans ceux des cosmétiques et des produits pharmaceutiques. Ainsi, la recherche effectuée dans le cadre de cette thèse a permis d'emprunter et d'appliquer une approche, celle du TTC dont la légitimité est établie, à l'exposition professionnelle, pour répondre à un problème de santé publique majeur dans le domaine de la santé et de la sécurité au travail. De plus, en développant des modèles pharmacocinétiques qui requièrent essentiellement l'information sur la structure moléculaire des substances, la recherche a pu développer des outils qui tiennent compte de la dose interne d'exposition, critère significatif dans l'évaluation et la caractérisation du risque sanitaire des populations de travailleurs.

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ANNEXE - CHAPITRE 3

Occupational TTCs for systemic substances. Supplementary Data.

	Name	CASRN	Log TLV	Log Pow	Log VP
		Class I			
1	(1-methylethenyl)-Benzene	98-83-9	1.68	3.44	2.41
2	1-Butene	106-98-9	2.76	2.17	5.39
3	1-Hexene	592-41-6	2.24	3.15	4.39
4	2,2-Dimethylbutane	75-83-2	3.25	3.18	4.62
5	2,2-Dimethylpentane	590-35-2	3.21	3.67	4.12
6	2,3-Dimethylbutane	79-29-8	3.25	3.14	4.48
7	2,3-Dimethylpentane	565-59-3	3.21	3.63	3.94
8	2,4-Dimethylpentane	108-08-7	3.21	3.63	4.10
9	2-Butene	107-01-7	2.76	2.09	5.36
10	2-Butoxyethyl acetate (EGBEA)	112-07-2	2.12	1.57	1.85
11	2-Diethylaminoethanol	100-37-8	0.98	0.05	1.94
12	2-Ethoxyethanol (EGEE)	110-80-5	1.27	-0.42	2.62
13	2-Ethoxyethyl acetate (EGEEA)	111-15-9	1.43	0.59	2.60
14	2-Isopropoxyethanol	109-59-1	2.03	0.00	2.38
15	2-Methoxyethanol (EGME)	109-86-4	-0.51	-0.91	2.87
16	2-Methoxyethyl acetate (EGMEA)	110-49-6	-0.32	0.10	2.87
17	2-Methylbutane	78-78-4	3.47	2.72	4.96
18	2-Methylhexane	591-76-4	3.21	3.71	3.94
19	2-Methylpentane	107-83-5	3.25	3.21	4.44
20	2-Oxetanone	57-57-8	1.17	-0.80	2.48
21	2-Propanol	67-63-0	2.69	0.28	3.82
22	3-Methylhexane	589-34-4	3.21	3.71	3.92
23	3-Methylpentane	96-14-0	3.25	3.21	4.39
24	4-Methoxyphenol	150-76-5	0.70	1.59	0.05
25	4-Vinyl cyclohexene	100-40-3	-0.35	3.73	3.25
26	Acetic acid	64-19-7	1.39	0.09	3.36
27	Acetone	67-64-1	2.77	-0.24	4.52
28	Acetophenone	98-86-2	1.69	1.67	1.64
29	Adipic acid	124-04-9	0.70	0.23	-2.77
30	Butene	25167-67-3	2.76	2.17	5.39
31	Carbon dioxide	124-38-9	3.95	0.83	6.37
32	Carbon monoxide	630-08-0	1.46	0.40	6.06
33	Catechol	120-80-9	1.35	1.03	-0.83
34	cis-2-Butene	590-18-1	2.76	2.09	5.,36
35	Citral	5392-40-5	1.49	3.45	1.09

36	Cumene	98-82-8	2.39	3.45	2.68
37	Cyclohexane	110-82-7	2.54	3.18	4.10
38	Cyclopentane	287-92-3	3.24	2.,68	4.62
39	Dibutyl phthalate	84-74-2	0.70	4.61	-1.52
40	Diethylene glycol monobutyl ether	112-34-5	1.82	0.29	0.16
41	Diethyl ketone	96-22-0	2.85	0.75	1.60
42	Ethyl acrylate	140-88-5	1.31	1.22	3.71
43	Ethyl benzene	100-41-4	1.94	3.03	3.00
44	Ethyl tert-butyl ether	637-92-3	2.02	1.92	4.23
45	Ethylene	74-85-1	2.36	1.27	6.62
46	Ethyl ether	60-29-7	3.08	1.05	4.86
47	Ethyl mercaptan	75-08-1	0.10	1.27	4.84
48	Heptane	142-82-5	3.21	3.78	3.79
49	Hydroquinone	123-31-9	0.,00	1.03	-2.66
50	Isobutene	115-11-7	2.76	2.23	5.47
51	Isopropyl acetate	108-21-4	2.62	1.28	3.91
52	Isopropylamine	75-31-0	1.08	0.27	4.90
53	Mesityl oxide	141-79-7	1.78	1.37	3.21
54	Methanol	67-56-1	2.42	-0.63	4.20
55	Methyl acetate	79-20-9	2.78	0.37	3.85
56	Methyl acrylate	96-33-3	0.85	0.73	4.06
57	Methylal	109-87-5	3.49	-0.19	4.74
58	Methyl cyclohexane	108-87-2	3.21	3.59	3.74
59	Methyl ethyl ketone (MEK)	78-93-3	2.77	0.26	4.12
60	Methyl formate	107-31-3	2.09	-0.17	4.90
61	Methyl isobutyl carbinol	108-11-2	2.02	1.68	2.70
62	Methyl isobutyl ketone	108-10-1	1.91	1.16	3.46
63	Methyl isopropyl ketone	563-80-4	1.85	0.67	3.86
64	Methyl mercaptan	74-93-1	-0.01	0.78	5.31
65	Methyl methacrylate	80-62-6	2.31	1.28	3.69
66	m-Xylene	108-38-3	2.64	3.09	2.95
67	n-Butyl lactate	138-22-7	1.48	0.80	1.36
68	Neopentane	463-82-1	3.47	2.69	5.24
69	n-Hexane	110-54-3	2.25	3.29	4.30
70	Nonane	111-84-2	3.02	4.76	2.82
71	o-Xylene	95-47-6	2.64	3.09	2.96
72	Pentane	109-66-0	3.47	2.80	4.84
73	Phenol	108-95-2	1.28	1.51	1.63
74	Pindone	83-26-1	-1.00	2.87	-2.76
75	Propylene	115-07-1	2.93	1.68	5.97
76	p-tert-Butyl toluene	98-51-1	0.78	4.45	1.90
77	p-Xylene	106-42-3	2.64	3.09	2.96

78	Styrene, monomer	100-42-5	1.93	2.89	2.83
79	Terephthalic acid	100-21-0	1.00	1.76	-2.80
80	Toluene	108-88-3	1.88	2.54	3.50
81	trans-2-Butene	624-64-6	2.76	2.09	5.36
82	Triethylamine	121-44-8	0.32	1.51	3.90
83	Vinyl acetate	108-05-4	1.55	0.73	4.20
		Class II			
1	Cyclohexanol	108-93-0	2.31	1.64	1.94
2	Diacetyl	431-03-8	-1.45	-1.34	3.97
3	Ethyl amyl ketone	541-85-5	1.72	2.15	2.66
4	Ethyl butyl ketone	106-35-4	2.37	1.73	2.89
5	Glyoxal	107-22-2	-1.00	-1.66	4.58
6	Hydrogenated terphenyls (nonirradiated)	61788-32-7	0.71	8.55	-1.00
7	Methyl n-butyl ketone	591-78-6	1.31	1.24	3.26
8	Methyl isoamyl ketone	110-12-3	1.97	1.66	2.95
9	o-Methylcyclohexanone	583-60-8	2.36	1.54	2.60
10	Pyrethrum	8003-34-7	0.70	6.15	-3.40
11	Quinone	106-51-4	-0.35	0.25	0.53
12	sec-Butanol	78-92-2	2.48	0.77	3.44
		Class III			
1	1,1,1,2-Tetrachloro-2,2-difluoroethane	76-11-9	2.92	3.41	3.70
2	1,1,2,2-Tetrabromoethane	79-27-6	0.15	2.55	0.91
3	1,1,2,2-Tetrachloro-1,2-difluoroethane	76-12-0	2.62	3.41	3.80
4	1,1,2,2-Tetrachloroethane	79-34-5	0.84	2.19	2.80
5	1,1,2-Trichloroethane	79-00-5	1.74	2.01	3.44
6	1,1,2-Trichloro-1,2,2-trifluoroethane	76-13-1	3.88	3.09	4.63
7	1,1-Dichloroethane	75-34-3	2.61	1.76	4.46
8	1,2 (cis)-dichloroethylene	156-59-2	2.90	1.98	4.53
9	1,2 (trans)-dichloroethylene	156-60-5	2.90	1.98	4.53
10	1,2-dichloroethylene	540-59-0	2.90	1.98	4.53
11	1,3,5-Triglycidyl-s-triazinetrione	2451-62-9	-1.30	1.21	-7.89
12	1,3-Dichloropropene	542-75-6	0.66	2.29	3.47
13	1,3-Dioxolane	646-06-0	1.78	-0.31	4.14
14	1,4-Dioxane	123-91-1	1.86	-0.32	3.73
15	1-Bromopropane	106-94-5	-0.30	2.16	4.26
16	1-Chloro-1-nitropropane	600-25-9	1.00	1.13	2.89
17	1-Chloro-2-propanol	127-00-4	0.59	0.53	2.81
18	1-Methyl naphthalene	90-12-0	0.46	3.72	0.69
19	1-Nitropropane	108-03-2	1.96	0.95	3.10
20	(2-Methoxymethylethoxy)propanol (DPGME)	34590-94-8	2.78	-0.35	1.30
21	2,4,5-T	93-76-5	1.00	3.26	-3.03
22	2,4,6-Trinitrotoluene (TNT)	118-96-7	-1.00	1.99	-2.64

23	2,4-D	94-75-7	1.00	2.62	-2.43
24	2,4-Pentanedione	123-54-6	2.01	0.05	3.06
25	2-Aminopyridine	504-29-0	0.28	0.53	1.11
26	2-Chloro-1-propanol	78-89-7	0.59	0.53	2.65
27	2-Chloropropionic acid	598-78-7	-0.35	0.76	2.00
28	2-Ethylhexanoic acid	149-57-5	0.70	2.96	0.92
29	2-Methyl naphthalene	91-57-6	0.46	3.72	0.66
30	2-Nitropropane	79-46-9	1.56	0.87	3.32
31	3,5-Dinitro-o-toluamide	148-01-6	0.00	0.19	-5.04
32	3,5-Nitro-o-toluidine	99-55-8	0.00	2.02	-1.11
33	4,4'-Methylene dianiline	101-77-9	-0.09	2.18	-3.56
34	Acrylamide	79-06-1	-1.52	-0.81	1.23
35	Acrylonitrile	107-13-1	0.64	0.21	4.11
36	Alachlor	15972-60-8	0.00	3.37	-2.56
37	Aldrin	309-00-2	-1.30	6.75	-3.60
38	Allyl chloride	107-05-1	0.50	1.93	4.67
39	Allyl glycidyl ether (AGE)	106-92-3	0.67	0.45	2.76
40	Amitrole	61-82-5	-0.70	-0.47	-1.01
41	Ammonium perfluorooctanoate	3825-26-1	-2.00	1.94	-2.02
42	Aniline	62-53-3	0.88	1.08	2.02
43	ANTU	86-88-4	-0.52	2.13	-3.83
44	Atrazine (& related symmetrical triazines)	1912-24-9	0.30	2.82	-2.42
45	Biphenyl	92-52-4	0.10	3.76	0.00
46	Bromacil	314-40-9	1.00	1.68	-4.84
47	Bromoform	75-25-2	0.71	1.79	2.85
48	Camphor, synthetic	76-22-2	1.10	3.04	0.15
49	Carbon disulfide	75-15-0	0.49	1.94	4.66
50	Carbon tetrabromide	558-13-4	0.13	2.80	1.39
51	Carbonyl fluoride	353-50-4	0.73	-1.34	6.38
52	Carbonyl sulfide	463-58-1	1.09	-1.33	6.04
53	Chlordane	57-74-9	-0.30	6.26	-2.57
54	Chlorinated camphene	8001-35-2	-0.30	6.79	-3.72
55	Chlorobenzene	108-90-7	1.66	2.64	3.09
56	Chlorobromomethane	74-97-5	3.02	1.43	4.28
57	Chlorodifluoromethane	75-45-6	3.55	0.89	5.94
58	Chloroform	67-66-3	1.69	1.52	4.40
59	Chloropicrin	76-06-2	-0.17	1.32	3.47
60	Crufomate	299-86-5	0.70	3.30	-2.30
61	Cyclonite	121-82-4	-0.30	0.68	-3.75
62	DDT	50-29-3	0.00	6.79	-3.00
63	Dichloroacetic acid	79-43-6	0.42	0.52	-0.05
64	Dichloroethyl ether	111-44-4	1.47	1.56	2.14

65	Dichlorofluoromethane	75-43-4	1.62	1.21	5.26
66	Dichloromethane	75-09-2	2.24	1.34	4.76
67	Dichlorotetrafluoroethane	76-14-2	3.84	2.78	5.34
68	Dieldrin	60-57-1	-1.00	5.45	-3.44
69	Diethanolamine	111-42-2	0.00	-1.71	-1.14
70	Difluorodibromomethane	75-61-6	2.93	1.99	5.00
71	Diglycidyl ether (DGE)	2238-07-5	-1.27	-0.85	2.59
72	Diisopropylamine	108-18-9	1.32	1.64	1.94
73	Dimethylaniline	121-69-7	1.39	2.17	1.82
74	Dimethyl disulfide	624-92-0	0.28	1.87	3.51
75	Dimethylformamide	68-12-2	1.48	-0.93	2.67
76	Dinitrobenzene, all isomers	99-65-0	0.01	1.63	-1.00
77	Dinitrobenzene	100-25-4	0.01	1.63	-2.06
78	Dinitrobenzene	528-29-0	0.01	1.63	-1.93
79	Dinitrobenzene	25154-54-5	0.01	1.63	-1.93
80	Dinitro-o-cresol	534-52-1	-0.70	2.27	-3.65
81	Dinitrotoluene	25321-14-6	-0.70	2.18	-0.54
82	Diphenylamine	122-39-4	1.00	3.29	-0.89
83	Diquat	85-00-7	-0.30	-2.82	-6.02
84	Diquat	2764-72-9	-0.30	2.36	-1.71
85	Disulfiram	97-77-8	0.30	3.67	-3.06
86	Endosulfan	115-29-7	-1.00	3.50	-3.78
87	Endrin	72-20-8	-1.00	5.45	-3.44
88	Enflurane	13838-16-9	2.75	2.06	4.48
89	Epichlorohydrin	106-89-8	0.28	0.63	3.38
90	Ethyl bromide	74-96-4	1.35	1.67	4.80
91	Ethyl chloride	75-00-3	2.42	1.58	5.21
92	Ethylenediamine	107-15-3	1.39	-1.62	3.38
93	Ethylene dichloride	107-06-2	1.61	1.83	4.00
94	Ethylene glycol dinitrate (EGDN)	628-96-6	-0.51	1.17	1.71
95	Ethyleneimine	151-56-4	-1.06	-0.28	4.49
96	Ethyl silicate	78-10-4	1.93	0.04	2.34
97	Formamide	75-12-7	1.27	-1.61	1.24
98	Glycidol	556-52-5	0.78	-1.09	2.87
99	Halothane	151-67-7	2.61	2.26	4.59
100	Heptachlor	76-44-8	-1.30	5.86	-1.50
101	Heptachlor epoxide	1024-57-3	-1.30	4.56	-2.92
102	Hexachlorobenzene	118-74-1	-2.70	5.86	-3.39
103	Hexachlorobutadiene	87-68-3	-0.67	4.72	1.53
104	Hexachloroethane	67-72-1	0.99	4.03	0.90
105	Hexachloronaphthalene	1335-87-1	-0.70	7.04	-3.16
106	Hexafluoroacetone	684-16-2	-0.17	0.60	5.74

107	Hexafluoropropylene	116-15-4	-0.21	2.12	5.77
108	Indene	95-13-6	1.38	3.25	2.07
109	Iodoform	75-47-8	0.99	3.03	0.50
110	Isopropyl glycidyl ether (IGE)	4016-14-2	2.38	0.52	3.45
111	Ketene	463-51-4	-0.07	-0.52	6.04
112	Lindane	58-89-9	-0.30	4.26	-1.17
113	Methoxychlor	72-43-5	1.00	5.67	-2.25
114	Methyl acethylene	74-99-7	3.21	1.04	5.69
115	Methylacrylonitrile	126-98-7	0.44	0.76	3.88
116	Methyl tert-butyl ether (MTBE)	1634-04-4	2.26	1.43	4.53
117	Methyl chloride	74-87-3	2.01	1.09	5.73
118	Methyl chloroform	71-55-6	3.28	2.68	4.17
119	Methyl iodide	74-88-4	1.06	1.59	4.73
120	Methyl silicate	681-84-5	0.79	-1.93	3.30
121	Metribuzin	21087-64-9	0.70	1.49	-2.16
122	m-Nitrotoluene	99-08-1	1.05	2.36	0.97
123	Morpholine	110-91-8	1.85	-0.56	3.16
124	m-Phenylenediamine	108-45-2	-1.00	-0.39	-0.60
125	m-Toluidine	108-44-1	0.94	1.62	1.61
126	Naphthalene	91-20-3	1.72	3.17	0.73
127	n-Butyl glycidyl ether (BGE)	2426-08-6	1.20	1.08	2.54
128	N-Ethylmorpholine	100-74-3	1.37	0.14	2.96
129	Nicotine	54-11-5	-0.30	1.00	0.63
130	N-Isopropylaniline	768-52-5	1.04	2.53	1.62
131	Nitrapyrin	1929-82-4	1.00	3.35	0.31
132	Nitrobenzene	98-95-3	0.70	1.81	1.45
133	Nitroethane	79-24-3	2.49	0.45	3.43
134	Nitroglycerin (NG)	55-63-0	-0.33	1.51	0.56
135	Nitromethane	75-52-5	1.70	-0.04	3.68
136	N,N-Dimethyl acetamide	127-19-5	1.55	-0.49	2.42
137	N-Methyl aniline	100-61-8	0.34	1.62	1.76
138	n-Propyl nitrate	627-13-4	2.03	1.74	3.51
139	N-Vinyl-2-pyrrolidone	88-12-0	-0.64	0.25	1.25
140	o-Anisidine	90-04-0	-0.30	1.16	1.15
141	o-Chlorinated diphenyl oxide	31242-93-0	-0.30	7.08	-4.10
142	o-Chlorostyrene	2039-87-4	2.45	3.54	1.93
143	Octachloronaphthalene	2234-13-1	-1.00	8.33	-4.94
144	o-Dichlorobenzene	95-50-1	2.18	3.28	2.11
145	o-Nitrotoluene	88-72-2	1.05	2.36	1.20
146	o-Phenylenediamine	95-54-5	-1.00	0.16	-2.15
147	o-Phthalonitrile	91-15-6	0.00	1.09	-0.97
148	o-Toluidine	95-53-4	0.94	1.62	1.68

149	p,p'-Oxybis(benzenesulfonyl hydrazide)	80-51-3	-1.00	0.08	-9.05
150	p-Anisidine	104-94-9	-0.30	1.16	0.41
151	Paraquat, as the cation	4685-14-7	-0.30	-0.56	-1.48
152	p-Dichlorobenzene	106-46-7	1.78	3.28	1.94
153	Pentachloronitrobenzene	1321-64-8	-0.30	6.39	-2.70
154	Pentachloronitrobenzene	82-68-8	-0.30	5.03	-2.44
155	Pentachlorophenol	87-86-5	-0.30	4.74	-2.84
156	Perfluorobutyl ethylene	19430-93-4	3.00	4.40	5.26
157	Phenyl ether, vapor	101-84-8	0.84	4.05	0.35
158	Phenyl glycidyl ether (PGE)	122-60-1	-0.21	1.61	0.68
159	Phenyl mercaptan	108-98-5	-0.35	2.69	2.34
160	Phosgene	75-44-5	-0.39	-0.71	5.26
161	Phthalic anhydride	85-44-9	0.78	2.07	-1.53
162	Picloram	1918-02-1	1.00	1.36	-4.37
163	Picric acid	88-89-1	-1.00	1.54	-4.29
164	Piperazine	110-85-0	-0.98	-0.80	1.98
165	p-Nitroaniline	100-01-6	0.48	1.47	-2.56
166	p-Nitrochlorobenzene	100-00-5	-0.19	2.46	0.17
167	p-Nitrotoluene	99-99-0	1.05	2.36	0.56
168	Propargyl alcohol	107-19-7	0.36	-0.42	3.12
169	Propylene dichloride	78-87-5	1.66	2.25	3.78
170	Propylene glycol dinitrate	6423-43-4	-0.47	1.59	1.70
171	Propyleneimine	75-55-8	-0.33	0.13	4.30
172	p-Toluidine	106-49-0	0.94	1.62	-0.73
173	Pyridine	110-86-1	0.51	0.80	3.41
174	Rotenone (commercial)	83-79-4	0.70	4.31	-7.03
175	Simazine	122-34-9	-0.30	2.40	-2.91
176	Stoddard solvent	8052-41-3	2.76	5.25	2,36
177	Strychnine	57-24-9	-0.82	1.85	-7.50
178	Sulfometuron methyl	74222-97-2	0.70	1.71	-8.45
179	tert-Amyl methyl ether (TAME)	994-05-8	1.92	1.92	4.00
180	tert-Butanol	75-65-0	2.48	0.73	3.80
181	Tetrachloroethylene	127-18-4	2.23	2.97	3.37
182	Tetrachloronaphthalene	1335-88-2	0.30	5.75	-2.20
183	Tetrafluoroethylene	116-14-3	0.91	1.21	6.28
184	Tetrahydrofuran	109-99-9	2.17	0.94	4.36
185	Tetramethyl succinonitrile	3333-52-6	0.44	1.11	-0.81
186	Tetranitromethane	509-14-8	-1.40	-2.05	3.20
187	Toluene-2,4- diisocyanate (or as a mixture)	584-84-9	-2.15	3.74	0.54
188	Toluene-2,6-diisocyanate (or as a mixture)	91-08-7	-2.15	3.74	1.09
189	Trichloronaphthalene	1321-65-9	0.70	5.10	-1.38
190	Trifluorobromomethane	75-63-8	3.78	1.59	6.07

191	Trimethyl phosphite	121-45-9	1.01	-0.73	3.48
192	Vinylcyclohexene dioxide	106-87-6	-0.24	1.13	1.27
193	Vinylidene chloride	75-35-4	1.30	2.12	4.90
194	Vinylidene fluoride	75-38-7	3.12	1.24	6.40
195	Warfarin	81-81-2	-1.00	2.23	-8.83

ANNEXE - CHAPITRE 4

Supplemental Material

A framework for application of quantitative property-property relationships (QPPRs) in physiologically based pharmacokinetic (PBPK) models for high-throughput prediction of internal dose of inhaled organic chemicals

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Supplemental Material Sections

Supplemental material 1 - Table 1. Human physiological data.

Supplemental material 1 - Table 2. Algorithmic expressions of the chemical-specific parameters used in the generic QPPR-based PBPK model.

Supplemental material 2 - Table 1. Descriptive statistics of the dataset used for the expansion of the applicability domain.

Supplemental material 3 - Table 1. References for the experimental data on the tissue:blood partition coefficients, maximal velocity (V_{max}) and Michäelis-Menten affinity constant (K_m).

Supplemental material 4. Algebraic and mass balance equations used in development of the generic QPPR-PBPK framework.

Supplemental material 5 – Figure 1. PBPK model simulations of human venous blood concentrations for four chemicals from the evaluation dataset (1,2,4- Trimethylbenzene (2 ppm); Dichloromethane (100 ppm); Ethylbenzene (33 ppm) and Toluene (17 ppm)). The predictions were performed using the QPPR-derived P_{ba} as well as setting E equals to 1 (lower solid line) or 0 (upper solid line). PBPK simulations obtained with the QPPR-derived CL_h are presented as dashed lines. Experimental data (symbols) were obtained from Beliveau *et al.* (2005).

Supplemental material 1.

Table 1. Human physiological parameter values used in the generic QPPR-PBPK model for data-poor organic chemicals

Parameter	Value
Body weight (kg)[a]	70
Flow rates[a]	
Cardiac output (L/hr/$Kg^{0.7}$)[a]	18
Alveolar ventilation (L/hr/$Kg^{0.7}$)[a]	18
Blood flow rates as a fraction of cardiac output[a]	
Adipose tissue	0.05
Slowly perfused tissues	0.25
Richly perfused tissues	0.44
Liver	0.26
Tissue volume as a fraction of body weight[a]	
Adipose tissue	0.19
Slowly perfused tissues	0.62
Richly perfused tissues	0.05
Liver	0.026
Neutral lipid equivalents as a fraction of tissue volume (F_{nle})[b]	
Adipose tissue	0.7986
Slowly perfused tissues	0.0378
Richly perfused tissues and liver	0.0473
Water equivalents as a fraction of tissue volume (F_{we})[b]	
Adipose tissue	0.1514
Slowly perfused tissues	0.7573
Richly perfused tissues and liver	0.7400

[a]Obtained from Tardif et al. (1997).
[b]Obtained from Poulin and Krishnan (1996).

Table 2. Algorithms for partition coefficients and biochemical rate constants used in the generic QPPR-PBPK model

Parameter	Algorithm	References
	Partition coefficient (P)	
$P_{blood:air}$ (P_{ba})	$10^{(6.96-1.04\times LogVP-0.533\times LogP_{ow}-0.00495\times MW)}$	Buist et al. (2012)
$P_{tissue:air}$ (P_{ta})	$(F_{nlet} \times P_{voa}) + (F_{wet} \times P_{wa})$	Poulin and Krishnan (1996)[a]
$P_{vegetable\ oil:air}$ (P_{voa})	$P_{vow} \times P_{wa}$	
$P_{vegetable\ oil:water}$ (P_{vow})	Oxygenated compounds $10^{(1.099\times \log P_{ow} - 1.31)}$ Non-Oxygenated compounds $10^{(1.0654\times LogP_{ow} - 0.232)}$	Poulin and Haddad (2012)
$P_{tissue:blood}$ (P_{tb})	P_{ta}/P_{ba}	
	Biochemical rate constant	
Hepatic clearance (CL_h, L/hr)	$CL_h = K_{el} \times V_d$	

MW, molecular weight (g/mol); P_{ow}, *n*-octanol:water partition coefficient (unitless); P_{wa}, water:air partition coefficient (unitless); VP, vapor pressure (P_a).

[a]The algorithm uses neutral lipid equivalent (F_{nlet}) and water equivalent (F_{wet}) content of tissues to predict tissue:air partition coefficients for humans. The tissue:air partition coefficients predicted were: P_{fa}, P_{sa}, P_{ra}, and P_{la} for fat:air, slowly perfused tissue:air, richly perfused tissue:air, and liver:air, respectively.

Supplemental material 2.

Table 1. Descriptive statistics of the dataset used for the expansion of the applicability domain

	Validation set (N = 40)					Expansion set (N = 249)				
	Parameter									
	MW	Log P_{ow}	Log VP	Log P_{aw}	K_{el} (min^{-1})	MW	Log P_{ow}	Log VP	Log P_{aw}	K_{el} (min^{-1})
Med	102.18	2.07	3.99	-0.41	0.0019	118.18	1.63	2.34	-2.66	0.0020
Min	14.23	-0.32	0.90	-3.48	0.00081	28.01	-2.82	-9.05	-14.99	0.0003
Max	252.73	4.27	6.62	2.43	0.0022	431.10	8.55	6.40	3.89	0.0091

K_{el}: elimination rate; Max: maximum; Med: median; Min: minimum; *MW*: molecular weight (g/mol); P_{aw}: air:water partition coefficient; P_{ow}: *n*-octanol:water partition coefficient; *VP*: vapor pressure.

Supplemental material 3.

Table 1. References for the experimental data on the tissue:blood partition coefficients, maximal velocity (V_{max}) and Michäelis-Menten affinity constant (K_m).

Chemical	P_{tb}	V_{max}, K_m
1,1,1,2-Tetrachloroethane	*	(Gargas et al. 1988)
1,1,2,2-Tetrachloroethane	*	(Gargas et al. 1988)
1,1,2-Trichloroethane	*	(Gargas et al. 1988)
1,2,4-Trimethylbenzene	(Hissink et al., 2007)	(Hissink et al., 2007)
1,1-Dichloroethane	*	(Gargas et al. 1990)
1,2-Dichloroethane	*	(Gargas et al. 1990)
1,1-Dichloroethylene	*	(Gargas et al. 1990)
1,2-Dichloroethylene (cis-)	*	(Gargas et al. 1990)
1,2-Dichloroethylene (trans-)	*	(Gargas et al. 1990)
1,4-Dioxane	(Pelekis and Krishnan, 2004)	(Pelekis and Krishnan, 2004)
2-Methylpentane	(Sarigiannis et al., 2017)	(Sarigiannis et al., 2017)
Benzene	(Sarigiannis et al., 2017)	(Haddad et al., 1999)
Bromochloromethane	*	(Gargas et al., 1986)
Bromodichloromethane	*	(Haddad et al., 2006)
Bromoform	*	(Haddad et al., 2006)
Carbon tetrachloride	(Pelekis and Krishnan, 2004)	(Gargas et al., 1990)
Chloroethane	*	(Gargas et al., 1990)
Chloroform	(Pelekis and Krishnan, 2004)	(Gargas et al., 1990)
Dibromochloromethane	*	(Haddad et al., 2006)
Dibromomethane	*	(Gargas et al., 1986)
Dichloromethane	(Sarigiannis et al., 2017)	(Gargas et al., 1990)
Ethylbenzene	(Pelekis and Krishnan, 2004)	(Haddad et al., 1999)
Ethylene	(Csanady et al., 2000)	(Csanady et al., 2000)
Furan	(Kedderis and Held, 1996)	(Kedderis and Held, 1996)
Halothane	(Williams et al., 1996)	(Williams et al., 1996)
Hexachloroethane	*	(Gargas et al., 1988)
Heptane	(Sarigiannis et al., 2017)	(Sarigiannis et al., 2017)
Hexane (n-)	(Sarigiannis et al., 2017)	(Dennison et al., 2003)
Isoprene	*	(Filser et al., 1996)
Methyl chloride	*	(Gargas et al., 1990)
Octane	*	(Sarigiannis et al., 2017)
Pentachloroethane	*	(Gargas et al., 1988)
Propylene	(Filser et al., 2000)	(Filser et al., 2000)
Styrene	(Ramsey and Andersen, 1984)	(Ramsey and Andersen, 1984)
Tetrachloroethylene	(Pelekis and Krishnan, 2004)	(Reitz et al., 1996)
Toluene	(Sarigiannis et al., 2017)	(Haddad et al., 1999)
Trichloroethylene	(Sarigiannis et al., 2017)	(Gargas et al., 1990)
Vinyl chloride	(Pelekis and Krishnan, 2004)	(Gargas et al., 1990)
Xylene (m-)	(Pelekis and Krishnan, 2004)	(Haddad et al., 1999)
Xylene (o-)	(Pelekis and Krishnan, 2004)	(Dennison et al., 2003)

*$P_{tb} = P_{ta}/P_{tb}$. Abraham et al. (2005) for P_{ba}; Meulenberg and Vijverberg (2000) for P_{ta}.

Supplemental material 4. Algebraic and mass balance equations used in development of the generic QPPR-PBPK framework.

1/ Equations used for each non-metabolizing tissue (adipose tissue, richly perfused tissues, slowly perfused tissues, liver)

Rate of change in the amount of chemical in each non-metabolizing tissue compartment

$$\frac{dA_t}{dT} = Q_t \times (CA - C_{vt})$$

Amount $A_t = \int_0^t \frac{dA_t}{dT}$

Concentration in tissue $C_t = \frac{A_t}{V_t}$

Concentration in venous blood leaving the tissue $C_{vt} = \frac{C_t}{P_{tb}}$

2/ Equations used for description of metabolism in the liver

Rate of change in the amount of chemical in liver $\frac{dA_l}{dT} = Q_l \times (CA - C_{vl}) - \frac{dA_{met}}{dT}$

The rate in the amount metabolized (A_{met}) was described as a first-order process as follows:

$$\frac{dA_{met}}{dT} = CL_h \times CA$$

3/ The mixed venous blood concentration has been calculated as follows:

$$CV = \frac{\sum_{i=1}^{4}(C_{vti} \times Q_{ti})}{QC}$$

4/ Arterial blood concentration is computed with the following equation:

$$CA = \frac{QP \times C_{inh} + QC \times CV}{\frac{QP}{P_{ba}} + QC}$$

Supplementary material 5.

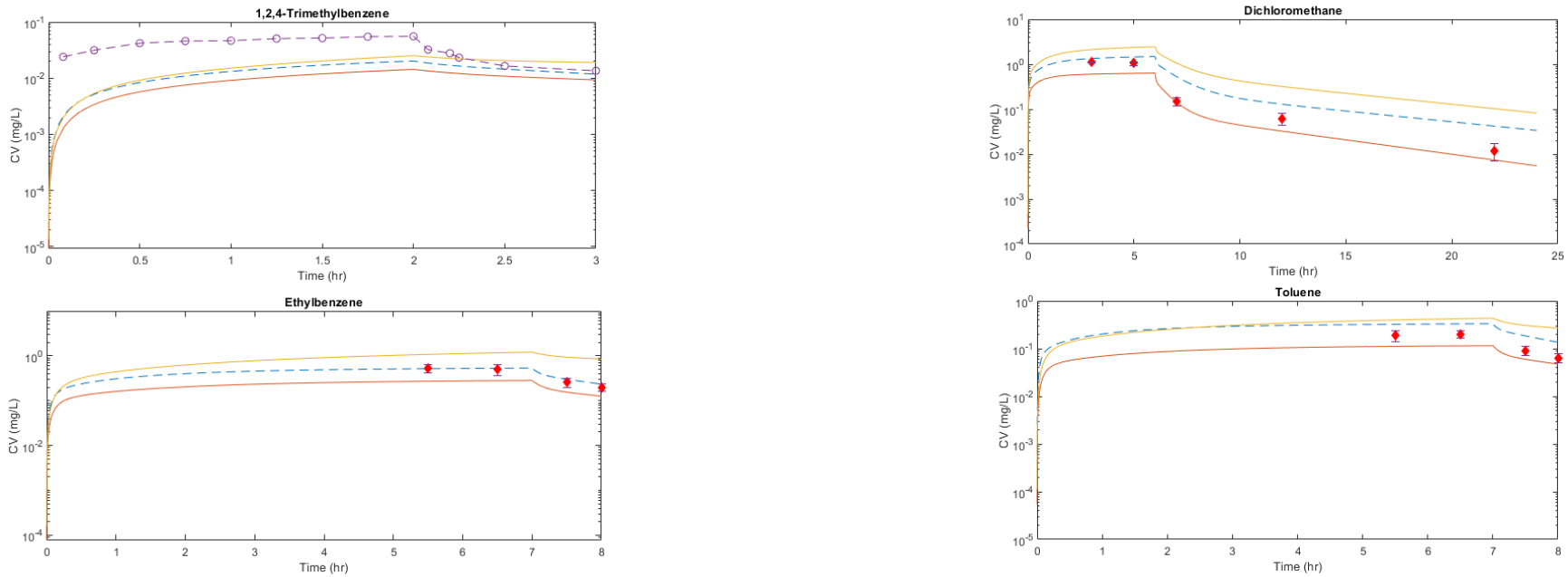

Figure 1. PBPK model simulations of human venous blood concentrations for four chemicals from the evaluation dataset (1,2,4-Trimethylbenzene (2 ppm); Dichloromethane (100 ppm); Ethylbenzene (33 ppm) and Toluene (17 ppm)). The predictions were performed using the QPPR-derived P_{ba} as well as setting E equals to 1 (lower solid line) or 0 (upper solid line). PBPK simulations obtained with the QPPR-derived CL_h are presented as dashed lines. Experimental data (symbols) were obtained from Beliveau *et al.*(2005).

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Supplemental material 6. PBPK model predictions of 24-hr area under the venous blood concentration vs time curve (AUC) for the 249 chemicals in the application dataset, obtained (i) by specifying predicted chemical-specific input parameters (first order elimination constant, K_{el} and hepatic clearance, CL_h) (AUC_{24}), (ii) by setting the hepatic extraction ratio E to its minimal value of 0 (AUC_E0) and (iii) by setting the hepatic extraction ratio E to its maximal value of 1 (AUC_E1).

	Name	Kel (min-1)	CL (L/hr)	AUC_{24}	AUC_E_0 (mmol/L.hr)	AUC_E_1
1	(1-methylethenyl)-Benzene	.0013	79.49	.00072	.00072	.00400
2	(2-Methoxymethylethoxy)propanol	.0027	79.49	.00041	.00041	.00117
3	1-Bromopropane	.0020	46.78	.00078	.00052	.00165
4	1-Butene	.0019	15.11	.00024	.00016	.00027
5	1-Chloro-1-nitropropane	.0020	6.33	.01322	.00092	.03706
6	1-Chloro-2-propanol	.0020	18.16	.00457	.00093	.01400
7	1-Hexene	.0023	40.23	.00043	.00030	.00062
8	1-Methylnaphthalene	.0012	33.23	.00208	.00082	.00868
9	1-Nitropropane	.0015	1.51	.04731	.00093	.10905
10	1,1,1,2-Tetrachloro-2,2-difluoroethane	.0014	79.49	.00028	.00028	.00056
11	1,1,2-Trichloro-1,2,2-trifluoroethane	.0017	79.49	.00008	.00008	.00012
12	1,1,2,2-Tetrabromoethane	.0019	79.49	.00067	.00067	.00296
13	1,1,2,2-Tetrachloro-1,2-difluoroethane	.0014	79.49	.00023	.00023	.00043
14	1,2-dichloroethylene	.0020	79.49	.00048	.00048	.00139
15	1,3-Dichloropropene	.0020	21.42	.00281	.00081	.00775
16	1,3-Dioxolane	.0022	1.16	.00737	.00092	.02205
17	1,3,5-Triglycidyl-s-triazinetrione	.0025	79.49	.00000	.00000	.00000
18	2-Aminopyridine	.0024	79.49	.00047	.00047	.00152
19	2-Butene	.0019	10.22	.00030	.00019	.00032
20	2-Butene (cis-)	.0019	10.22	.00030	.00019	.00032
21	2-Butene (trans-)	.0019	10.22	.00030	.00019	.00032
22	2-Butoxyethyl acetate (EGBEA)	.0044	16.48	.00564	.00093	.03466
23	2-Chloro-1-propanol	.0020	12.71	.00673	.00093	.02000
24	2-Chloropropionic acid	.0034	47.55	.00169	.00092	.00930
25	2-Diethylaminoethanol	.0035	79.49	.00032	.00032	.00080
26	2-Ethoxyethanol (EGEE)	.0029	18.09	.00497	.00093	.02060
27	2-Ethoxyethyl acetate (EGEEA)	.0041	20.73	.00441	.00093	.02500
28	2-Ethylhexanoic acid	.0021	74.54	.00087	.00080	.00733
29	2-Isopropoxyethanol	.0027	10.37	.00890	.00093	.03383
30	2-Methoxyethanol (EGME)	.0030	24.25	.00362	.00093	.01592
31	2-Methoxyethyl acetate (EGMEA)	.0044	79.49	.00080	.00080	.00436
32	2-Methylbutane	.0018	6.96	.00031	.00019	.00032
33	2-Methylhexane	.0019	12.73	.00070	.00036	.00080
34	2-Methylnaphthalene	.0012	31.91	.00217	.00082	.00887
35	2-Nitropropane	.0016	1.71	.03913	.00092	.08813
36	2-Oxetanone	.0039	1.02	.09680	.000935	.66669
37	2-Propanol	.0021	23.42	.00341	.00092	.01095
38	2,2-Dimethylbutane	.0017	16.52	.00032	.00020	.00035
39	2,2-Dimethylpentane	.0019	18.98	.00045	.00028	.00053
40	2,3-Dimethylbutane	.0018	13.83	.00046	.00027	.00051
41	2,3-Dimethylpentane	.0019	18.79	.00069	.00038	.00086
42	2,4-D	.0018	79.49	.03821	.00093	.11562
43	2,4-Dimethylpentane	.0019	24.76	.00047	.00029	.00058
44	2,4-Pentanedione	.0016	7.77	.01053	.00093	.02601
45	2,4,5-T	.0016	79.49	.00235	.00085	.01054
46	2,4,6-Trinitrotoluene	.0016	79.49	.16583	.00093	.94912
47	3-Methylhexane	.0019	25.06	.00062	.00036	.00081
48	3-Methylpentane	.0022	12.84	.00052	.00029	.00058
49	3,5-Dinitro-o-toluamide	.0020	79.49	.00593	.00093	.01790
50	4-Methoxyphenol	.0014	61.59	.01048	.00093	.02460
51	4-Vinyl cyclohexene	.0017	79.49	.00057	.00057	.00206
52	4,4'-Methylene dianiline	.0018	79.49	.00078	.00078	.00604
53	5-Nitro-o-toluidine	.0018	79.49	.00755	.00093	.02293

54	Acetic acid	.0030	79.49	.00059	.00059	.00210
55	Acetone	.0021	23.59	.00322	.00090	.00987
56	Acetophenone	.0017	2.08	.04282	.00093	.12027
57	Acrylamide	.0023	79.49	.00143	.00087	.00609
58	Acrylonitrile	.0020	4.26	.01655	.00091	.04071
59	Adipic acid	.0024	79.49	.00585	.00093	.02042
60	Alachlor	.0019	79.49	.00078	.00078	.00606
61	Aldrin	.0011	79.49	.00003	.00003	.00005
62	Allyl chloride	.0020	20.00	.00110	.00051	.00154
63	Amitrole	.0022	79.49	.00015	.00015	.00029
64	Ammonium perfluorooctanoate	.0007	79.49	.00044	.00044	.00138
65	Amyl methyl ether (tert-)	.0020	8.13	.00394	.00077	.00597
66	Aniline	.0022	15.49	.00545	.00092	.01999
67	Anisidine (o-)	.0022	2.92	.03233	.00093	.11125
68	Anisidine (p-)	.0022	33.87	.01539	.00093	.04941
69	ANTU	.0015	79.49	.15771	.00093	.71830
70	Atrazine	.0015	79.49	.00068	.00068	.00322
71	Biphenyl	.0012	13.06	.00547	.00089	.01566
72	Bromacil	.0026	79.49	.12395	.00093	1.94409
73	Butanol (sec-)	.0020	15.07	.00543	.00092	.01588
74	Butanol (tert-)	.0020	33.14	.00225	.00089	.00732
75	Butene	.0019	15.11	.00024	.00016	.00027
76	Butyl glycidyl ether (n-)	.0025	3.76	.02401	.00093	.08537
77	Butyl lactate (n-)	.0039	2.72	.03630	.00093	.26370
78	Butyl toluene (p-tert-)	.0011	79.49	.00058	.00058	.00215
79	Camphor, synthetic	.0046	3.02	.03267	.00093	.29291
80	Carbon disulfide	.0018	19.28	.00113	.00052	.00157
81	Carbon monoxide	.0021	79.49	.00000	.00000	.00001
82	Carbon tetrabromide	.0019	79.49	.00077	.00077	.00596
83	Carbonyl fluoride	.0020	3.17	.00158	.00053	.00169
84	Carbonyl sulfide	.0020	.51	.00393	.00071	.00401
85	Catechol	.0083	79.49	.00205	.00093	.02551
86	Chlordane	.0011	79.49	.00006	.00006	.00010
87	Chlorinated camphene	0.011	79.49	.00001	.00001	.00001
88	Chlorinated diphenyl oxide (o-)	.0006	79.49	.00004	.00004	.00007
89	Chlorobenzene	.0013	30.61	.00203	.00079	.00673
90	Chlorodifluoromethane	.0019	5.48	.00024	.00015	.00025
91	Chloropicrin	.0020	1.19	.01748	.00088	.02218
92	Chlorostyrene (o-)	.0011	72.17	.00085	.00076	.00534
93	Citral	.0022	10.25	.00830	.00093	.03046
94	Cumene	.0016	75.63	.00079	.00074	.00507
95	Cyclohexane	.0017	48.21	.00061	.00043	.00112
96	Cyclohexanol	.0018	4.89	.01774	.00093	.04884
97	Cyclonite	.0025	79.49	.05888	.00093	.28566
98	Cyclopentane	.0018	26.99	.00057	.00034	.00075
99	DDT	.0007	79.49	.00001	.00001	.00001
100	Diacetyl	.0023	4.30	.02083	.00093	.06824
101	Dibutyl phthalate	.0040	79.49	.00051	.00051	.00172
102	Dichloroacetic acid	.0033	79.49	.01020	.00093	.04716
103	Dichlorobenzene (o-)	.0012	69.11	.00090	.00076	.00559
104	Dichlorobenzene (p-)	.0012	37.90	.00177	.00080	.00760
105	Dichloroethyl ether	.0023	5.25	.01714	.00093	.05657
106	Dichlorofluoromethane	.0018	14.68	.00061	.00033	.00070
107	Dichlorotetrafluoroethane	.0018	40.12	.00003	.00003	.00004
108	Dieldrin	.0012	79.49	.00035	.00035	.00094
109	Diethanolamine	.0056	79.49	.00748	.00093	.05953
110	Diethyl ketone	.0025	.67	.14614	.00093	4.26177
111	Diethylene glycol monobutyl ether	.0025	79.49	.00842	.00093	.02999
112	Difluorodibromomethane	.0019	79.49	.00009	.00009	.00014
113	Diglycidyl ether (DGE)	.0028	79.49	.00040	.00040	.00115
114	Diisopropylamine	.0021	2.93	.03105	.00093	.10338
115	Dimethyl disulfide	.0020	12.39	.00522	.00087	.01358
116	Dimethylacetamide (N,N-)	.0023	79.49	.00051	.00051	.00167
117	Dimethylaniline	.0023	20.62	.00393	.00090	.01763
118	Dimethylformamide	.0023	41.81	.00183	.00090	.00732
119	Dinitro-o-cresol	.0023	6.75	.01339	.00093	.04763
120	Dinitrobenzene	.0018	55.33	.18324	.00093	.18601
121	Dinitrobenzene (m-)	.0018	61.71	.06499	.00093	.21531
122	Dinitrobenzene (o-)	.0018	55.33	.18324	.00093	2.18601
123	Dinitrobenzene (p-)	.0018	37.66	.20176	.00093	4.41451

124	Dinitrotoluene	.0016	75.12	.00903	.00093	.02534
125	Diphenylamine	.0021	79.49	.00068	.00068	.00319
126	Diquat	.0091	79.49	.0408	.00093	6.15365
127	Diquat	.0091	79.49	.00010	.00010	.00018
128	Disulfiram	.0024	44.87	.00165	.00085	.01090
129	Endosulfan	.0014	2.21	.03800	.00093	.09421
130	Endrin	.0012	79.49	.00035	.00035	.00094
131	Enflurane	.0020	11.03	.00057	.00031	.00064
132	Epichlorohydrin	.0020	5.54	.01483	.00092	.04082
133	Ethyl acrylate	.0024	3.82	.01369	.00089	.02795
134	Ethyl amyl ketone	.0025	6.76	.01182	.00092	.03759
135	Ethyl bromide	.0021	36.32	.00068	.00042	.00107
136	Ethyl butyl ketone	.0026	4.48	.01752	.00092	.05456
137	Ethyl ether	.0024	7.70	.00247	.00066	.00314
138	Ethyl mercaptan	.0014	5.11	.00244	.00065	.00285
139	Ethyl morpholine (N-)	.0027	79.49	.00066	.00066	.00265
140	Ethyl silicate	.0027	1.80	.05195	.00093	.24777
141	Ethyl tert-butyl ether	.0020	9.81	.00253	.00069	.00350
142	Ethylene glycol dinitrate (EGDN)	.0046	8.34	.01156	.00093	.07585
143	Ethylenediamine	.0034	79.49	.00013	.00013	.00025
144	Ethyleneimine	.0035	66.99	.00107	.00087	.00642
145	Formamide	.0025	79.49	.00339	.00093	.01293
146	Glyoxal	.0023	79.49	.00003	.00003	.00005
147	Heptachlor	.0011	79.49	.00014	.00014	.00027
148	Heptachlor epoxide	.0012	79.49	.00048	.00048	.00152
149	Hexachlorobenzene	.0009	.29	.33236	.00093	1.42094
150	Hexachlorobutadiene	.0012	79.49	.00034	.00034	.00090
151	Hexachloronaphthalene	.0004	79.49	.00003	.00003	.00005
152	Hexafluoroacetone	.0003	4.67	.00022	.00014	.00023
153	Hexafluoropropylene	.0009	1.73	.00004	.00003	.00004
154	Hydrogenated terphenyls	.0011	79.49	.00005	.00005	.00009
155	Hydroquinone	.0016	79.49	.03273	.00093	.08439
156	Indene	.0018	63.64	.00103	.00080	.00725
157	Iodoform	.0020	79.49	.00051	.00051	.00170
158	Isobutene	.0020	24.55	.00018	.00013	.00020
159	Isopropyl acetate	.0030	8.06	.00690	.00087	.01561
160	Isopropylamine	.0023	79.49	.00067	.00067	.00273
161	Isopropylaniline (N-)	.0022	79.49	.00067	.00067	.00302
162	Ketene	.0020	79.49	.00001	.00001	.00002
163	Lindane	.0018	79.49	.00032	.00032	.00082
164	Mesityl oxide	.0020	6.71	.01161	.00092	.03095
165	Methanol	.0023	28.57	.00283	.00092	.01016
166	Methoxychlor	.0011	79.49	.00002	.00002	.00003
167	Methyl acetate	.0038	4.85	.01615	.00092	.06149
168	Methyl acethylene	.0018	12.78	.00056	.00031	.00064
169	Methyl acrylate	.0025	5.75	.01036	.00089	.02385
170	Methyl chloroform	.0019	79.49	.00038	.00038	.00093
171	Methyl cyclohexane	.0016	40.26	.00075	.00047	.00133
172	Methyl cyclohexanone (o-)	.0044	5.37	.01699	.00093	.09709
173	Methyl ethyl ketone (MEK)	.0020	8.48	.00876	.00091	.02254
174	Methyl formate	.0021	7.13	.00700	.00086	.01361
175	Methyl iodide	.0021	48.67	.00053	.00039	.00093
176	Methyl isoamyl ketone	.0026	3.72	.02022	.00092	.06054
177	Methyl isobutyl carbinol	.0021	4.72	.01772	.00092	.05185
178	Methyl isobutyl ketone	.0018	2.95	.02066	.00091	.04432
179	Methyl isopropyl ketone	.0019	4.70	.01400	.00091	.03196
180	Methyl mercaptan	.0015	6.27	.00175	.00057	.00201
181	Methyl methacrylate	.0018	3.05	.01508	.00089	.02699
182	Methyl n-butyl ketone	.0023	3.95	.01888	.00092	.05221
183	Methyl silicate	.0031	2.61	.03708	.00093	.19289
184	Methyl tert-butyl ether (MTBE)	.0018	12.16	.00243	.00069	.00362
185	Methylacrylonitrile	.0018	4.54	.01445	.00091	.03257
186	Methylal	.0027	8.20	.00713	.00087	.01656
187	Methylaniline (N-)	.0024	14.15	.00605	.00092	.02470
188	Metribuzin	.0021	79.49	.00345	.00092	.01189
189	Morpholine	.0037	29.78	.00294	.00093	.01589
190	Naphthalene	.0013	5.58	.01370	.00093	.03380
191	Neopentane	.0018	4.73	.00017	.00011	.00017
192	Nicotine	.0023	79.49	.00041	.00041	.00123
193	Nitrapyrin	.0015	79.49	.00067	.00067	.00309

194	Nitroaniline (p-)	.0019	79.49	.11677	.00093	.60564
195	Nitrobenzene	.0020	1.27	.07421	.00093	.29123
196	Nitrochlorobenzene (p-)	.0013	2.34	.03481	.00093	.08066
197	Nitroethane	.0016	2.46	.03111	.00093	.07409
198	Nitroglycerin (NG)	.0072	79.49	.00092	.00092	.01156
199	Nitromethane	.0017	3.67	.02207	.00093	.05529
200	Nitrotoluene (m-)	.0019	4.52	.01950	.00093	.05904
201	Nitrotoluene (o-)	.0019	5.65	.01536	.00093	.04672
202	Nitrotoluene (p-)	.0019	2.99	.03032	.00093	.09335
203	Nonane	.0014	37.41	.00097	.00055	.00193
204	Octachloronaphthalene	.0004	79.49	.00001	.00001	.00002
205	Oxybis(p,p'-)	.0038	79.49	.00349	.00093	.01903
206	Paraquat	.0091	79.49	.00019	.00019	.00037
207	Pentachloronaphthalene	.0004	79.49	.00015	.00015	.00028
208	Pentachloronitrobenzene	.0010	79.49	.00073	.00073	.00423
209	Pentachlorophenol	.0011	79.49	.00032	.00032	.00084
210	Pentane	.0023	9.90	.00037	.00022	.00039
211	Perfluorobutyl ethylene	.0006	79.49	.00000	.00000	.00000
212	Phenol	.0014	21.22	.00343	.00090	.00907
213	Phenyl ether	.0012	13.73	.00518	.00089	.01498
214	Phenyl glycidyl ether	.0021	5.13	.01776	.00093	.05582
215	Phenyl mercaptan	.0020	73.23	.00088	.00079	.00712
216	Phenylenediamine (m-)	.0025	79.49	.02772	.00093	.10628
217	Phenylenediamine (o-)	.0025	79.49	.15370	.00093	10.01522
218	Phthalonitrile (o-)	.0008	5.42	.01142	.00092	.02083
219	Picloram	.0025	79.49	.00051	.00051	.00172
220	Pindone	.0028	79.49	.00020	.00020	.00040
221	Propargyl alcohol	.0023	13.89	.00633	.00093	.02119
222	Propyl nitrate (n-)	.0037	3.76	.01240	.00088	.02372
223	Propylene dichloride	.0019	.47	.00589	.00077	.00607
224	Propylene glycol dinitrate	.0052	1.33	.07024	.00093	1.08534
225	Propyleneimine	.0033	79.49	.00078	.00078	.00407
226	Pyridine	.0023	39.12	.00193	.00087	.00837
227	Quinone	.0021	.52	.18774	.00093	10.83372
228	Rotenone	.0013	79.49	.00008	.00008	.00014
229	Simazine	.0016	79.49	.00181	.00083	.00920
230	Strychnine	.0026	79.49	.03348	.00093	.14093
231	Sulfometuron methyl	.0036	79.49	.10596	.00093	8.79901
232	Terephthalic acid	.0029	79.49	.00046	.00046	.00147
233	Tetrachloronaphthalene	.0004	79.49	.00035	.00035	.00094
234	Tetrafluoroethylene	.0019	3.20	.00006	.00004	.00006
235	Tetrahydrofuran	.0020	25.49	.00251	.00084	.00653
236	Tetramethyl succinonitrile	.0019	79.49	.05174	.00093	.17183
237	Tetranitromethane	.0022	.59	.15521	.00093	1.77382
238	Toluidine (m-)	.0021	44.75	.00163	.00084	.00930
239	Toluidine (o-)	.0021	43.88	.00166	.00085	.00941
240	Toluidine (p-)	.0021	9.15	.00944	.00093	.03283
241	Trichloronaphthalene	.0004	75.77	.00069	.00065	.00284
242	Triethylamine	.0030	79.49	.00072	.00072	.00409
243	Trifluorobromomethane	.0009	6.70	.00004	.00003	.00004
244	Vinyl acetate	.0025	2.71	.01270	.00088	.01961
245	Vinyl-2-pyrrolidone (N-)	.0021	30.28	.00814	.00093	.02510
246	Vinylcyclohexene dioxide	.0019	26.06	.00303	.00092	.00954
247	Vinylidene fluoride	.0018	5.05	.00007	.00005	.00007
248	Warfarin	.0018	79.49	.22394	.00093	78280.17
249	Xylene (p-)	.0017	53.52	.00117	.00076	.00574

ANNEXE - CHAPITRE 5

Supplemental material. PBPK model predictions of the three measures of internal dose, for each of the 276 studied chemicals, obtained in this study: daily rate of the amount of parent chemical metabolized ($RMET_{24}$), 24-hr area under the venous blood concentration versus time curve (AUC_{24}) and maximum venous blood concentration at the end of an 8-hr workshift ($CMAX_8$).

Name	LogRMETmmold	LogAUCmmold	LogCMAXmmol
(1-methylethenyl)-Benzene	0.43	-1.59	-2.56
(2-Methoxymethylethoxy)propanol (DPGME)	0.88	-1.24	-2.42
1-Bromopropane	-2.14	-3.87	-4.80
1-Butene	0.01	-1.19	-2.10
1-Chloro-1-nitropropane	-0.55	-1.40	-2.44
1-Chloro-2-propanol	-0.81	-2.15	-3.22
1-Hexene	0.09	-1.56	-2.48
1-Methylnaphthalene	-0.85	-2.42	-3.42
1-Nitropropane	0.44	0.21	-0.80
1,1-Dichloroethane	0.75	-0.69	-1.62
1,1,1,2-Tetrachloro-2,2-difluoroethane	0.66	-1.36	-2.28
1,1,2-Trichloro-1,2,2-trifluoroethane	0.99	-1.02	-1.93
1,1,2-Trichloroethane	0.40	-1.62	-2.57
1,1,2,2-Tetrabromoethane	-1.57	-3.60	-4.63
1,1,2,2-Tetrachloro-1,2-difluoroethane	0.26	-1.77	-2.69
1,1,2,2-Tetrachloroethane	-0.54	-2.52	-3.48
1,2-dichloroethylene	1.30	-0.71	-1.64
1,2-Dichloroethylene (cis-)	1.30	-0.71	-1.64
1,2-Dichloroethylene (trans-)	1.30	-0.71	-1.64
1,3-Dichloropropene	-0.82	-2.18	-3.14
1,3-Dioxolane	0.45	-0.66	-1.70
1,3,5-Triglycidyl-s-triazinetrione	-3.95	-8.34	-9.64
1,4-Dioxane	0.49	-0.98	-2.04
2-Aminopyridine	-1.33	-3.40	-4.56
2-Butene	-0.08	-1.11	-2.01
2-Butene (cis-)	-0.08	-1.11	-2.01
2-Butene (trans-)	-0.08	-1.11	-2.01
2-Butoxyethyl acetate (EGBEA)	0.53	-0.74	-1.70
2-Chloro-1-propanol	-0.81	-1.99	-3.05
2-Chloropropionic acid	-1.78	-3.56	-4.56
2-Diethylaminoethanol	-0.94	-3.15	-4.33
2-Ethoxyethanol (EGEE)	-0.08	-1.42	-2.43
2-Ethoxyethyl acetate (EGEEA)	-0.08	-1.47	-2.43
2-Ethylhexanoic acid	-0.90	-2.86	-3.83
2-Isopropoxyethanol	0.61	-0.47	-1.49
2-Methoxyethanol (EGME)	-1.78	-3.25	-4.26
2-Methoxyethyl acetate (EGMEA)	-1.81	-3.81	-4.88
2-Methylbutane	0.36	-0.50	-1.41
2-Methylhexane	0.61	-0.51	-1.42
2-Methylnaphthalene	-0.85	-2.40	-3.41
2-Methylpentane	0.56	-0.61	-1.51
2-Nitropropane	0.00	-0.28	-1.27
2-Oxetanone	-1.08	-1.09	-1.99
2-Propanol	1.48	0.02	-1.04
2,2-Dimethylbutane	0.47	-0.77	-1.68
2,2-Dimethylpentane	0.61	-0.69	-1.60
2,3-Dimethylbutane	0.56	-0.61	-1.51
2,3-Dimethylpentane	0.81	-0.49	-1.40
2,4-D	-0.76	-1.15	-2.20
2,4-Dimethylpentane	0.76	-0.66	-1.58
2,4-Pentanedione	0.56	-0.40	-1.50
2,4,5-T	-0.87	-2.41	-3.42

2,4,6-Trinitrotoluene	-2.74	-2.52	-3.48
3-Methylhexane	0.91	-0.52	-1.44
3-Methylpentane	0.58	-0.55	-1.46
3,5-Dinitro-o-toluamide	-1.77	-3.01	-4.07
4-Methoxyphenol	-0.86	-1.78	-2.89
4-Vinyl cyclohexene	-1.82	-3.84	-4.78
4,4'-Methylene dianiline	-1.84	-3.86	-4.82
5-Nitro-o-toluidine	-1.62	-2.69	-3.76
Acetic acid	0.06	-1.98	-3.14
Acetone	1.54	0.08	-0.96
Acetophenone	0.18	-0.17	-1.22
Acrylamide	-2.79	-4.62	-5.67
Acrylonitrile	-0.47	-1.15	-2.09
Adipic acid	-0.87	-2.12	-3.16
Alachlor	-1.89	-3.90	-4.86
Aldrin	-3.66	-6.75	-8.03
Allyl chloride	-1.52	-2.85	-3.77
Amitrole	-2.66	-5.13	-6.36
Ammonium perfluorooctanoate	-4.31	-6.40	-7.55
Amyl methyl ether (tert-)	-0.09	-1.04	-1.96
Aniline	-0.17	-1.40	-2.44
Anisidine (o-)	-1.79	-2.30	-3.33
Anisidine (p-)	-1.80	-2.63	-3.67
ANTU	-2.21	-2.01	-2.99
Atrazine	-1.54	-3.57	-4.59
Biphenyl	-1.25	-2.39	-3.46
Bromacil	-0.80	-0.71	-1.61
Bromoform	-0.94	-2.52	-3.50
Butanol (sec-)	1.17	-0.08	-1.14
Butanol (tert-)	1.16	-0.45	-1.52
Butene	0.01	-1.19	-2.10
Butyl glycidyl ether (n-)	-0.34	-0.97	-1.96
Butyl lactate (n-)	-0.07	-0.55	-1.48
Butyl toluene (p-tert-)	-0.64	-2.68	-3.75
Camphor, synthetic	-0.47	-0.96	-1.88
Carbon disulfide	-1.52	-2.84	-3.75
Carbon monoxide	-0.34	-4.10	-5.40
Carbon tetrabromide	-1.52	-3.53	-4.49
Carbonyl fluoride	-1.93	-2.49	-3.39
Carbonyl sulfide	-2.00	-1.70	-2.61
Catechol	-0.07	-1.78	-2.70
Chlordane	-2.69	-5.50	-6.78
Chlorinated camphene	-2.75	-6.56	-7.86
Chlorinated diphenyl oxide (o-)	-3.01	-5.98	-7.26
Chlorobenzene	0.30	-1.23	-2.21
Chlorobromomethane	1.26	-0.23	-1.17
Chlorodifluoromethane	0.16	-0.61	-1.52
Chloroform	-0.31	-1.58	-2.50
Chloropicrin	-2.62	-2.72	-3.62
Chlorostyrene (o-)	1.15	-0.80	-1.76
Citral	-0.12	-1.15	-2.18
Cumene	1.11	-0.86	-1.81
Cyclohexane	0.72	-1.02	-1.95
Cyclohexanol	0.88	0.15	-0.92
Cyclonite	-2.03	-2.29	-3.27
Cyclopentane	1.09	-0.38	-1.30
DDT	-2.37	-6.05	-7.35
Diacetyl	-2.82	-3.51	-4.53
Dibutyl phthalate	-1.36	-3.42	-4.54
Dichloroacetic acid	-1.07	-2.11	-3.09
Dichlorobenzene (o-)	0.85	-1.08	-2.04
Dichlorobenzene (p-)	0.43	-1.20	-2.20
Dichloroethyl ether	-0.11	-0.87	-1.90
Dichlorofluoromethane	-0.97	-2.18	-3.08
Dichloromethane	0.28	-0.97	-1.89
Dichlorotetrafluoroethane	0.21	-1.44	-2.36
Dieldrin	-3.38	-5.53	-6.70
Diethanolamine	-1.40	-2.58	-3.50
Diethyl ketone	1.52	1.69	0.79
Diethylene glycol monobutyl ether	0.21	-0.89	-1.92

Difluorodibromomethane	0.08	-1.94	-2.85
Diglycidyl ether (DGE)	-3.13	-5.26	-6.43
Diisopropylamine	0.21	-0.27	-1.29
Dimethyl disulfide	-1.10	-2.21	-3.18
Dimethylacetamide (N,N-)	-0.01	-2.07	-3.25
Dimethylaniline	0.22	-1.13	-2.15
Dimethylformamide	0.20	-1.53	-2.59
Dinitro-o-cresol	-2.40	-3.26	-4.29
Dinitrobenzene	-1.59	-1.33	-2.24
Dinitrobenzene (m-)	-1.61	-1.80	-2.84
Dinitrobenzene (o-)	-1.59	-1.33	-2.24
Dinitrobenzene (p-)	-1.59	-1.29	-2.19
Dinitrotoluene	-2.41	-3.39	-4.47
Diphenylamine	-0.40	-2.43	-3.45
Diquat	-2.91	-3.31	-4.21
Diquat	-3.34	-5.97	-7.22
Disulfiram	-1.26	-2.97	-3.96
Endosulfan	-3.06	-3.41	-4.51
Endrin	-3.38	-5.53	-6.70
Enflurane	-0.27	-1.35	-2.25
Epichlorohydrin	-1.16	-1.97	-3.00
Ethyl acrylate	-0.44	-1.07	-1.99
Ethyl amyl ketone	0.11	-0.74	-1.73
Ethyl benzene	0.65	-1.08	-2.04
Ethyl bromide	-0.72	-2.33	-3.25
Ethyl butyl ketone	0.79	0.11	-0.86
Ethyl chloride	-0.68	-2.15	-3.07
Ethyl ether	0.97	0.03	-0.88
Ethyl mercaptan	-2.13	-2.87	-3.77
Ethyl morpholine (N-)	-0.19	-2.21	-3.35
Ethyl silicate	0.19	-0.10	-1.06
Ethyl tert-butyl ether	-0.12	-1.15	-2.06
Ethylene	-0.89	-1.94	-2.84
Ethylene dichloride	0.30	-1.71	-2.66
Ethylene glycol dinitrate (EGDN)	-2.07	-3.05	-3.99
Ethylenediamine	-0.43	-2.95	-4.19
Ethyleneimine	-1.77	-3.73	-4.72
Formamide	0.21	-1.28	-2.32
Glyoxal	-2.91	-5.97	-7.26
Halothane	-0.07	-1.87	-2.78
Heptachlor	-3.57	-6.05	-7.29
Heptachlor epoxide	-3.19	-5.27	-6.41
Heptane	0.89	-0.41	-1.33
Hexachlorobenzene	-4.24	-3.71	-4.67
Hexachlorobutadiene	-2.58	-4.72	-5.88
Hexachloroethane	-0.52	-2.50	-3.46
Hexachloronaphthalene	-3.03	-6.13	-7.41
Hexafluoroacetone	-3.91	-4.65	-5.55
Hexafluoropropylene	-5.15	-5.40	-6.30
Hexane (n-)	-0.41	-1.50	-2.40
Hydrogenated terphenyls	-1.48	-4.35	-5.63
Hydroquinone	-1.47	-1.95	-3.03
Indene	0.18	-1.70	-2.67
Iodoform	-0.88	-2.95	-4.07
Isobutene	0.11	-1.31	-2.22
Isopropyl acetate	0.90	-0.06	-0.98
Isopropylamine	0.06	-1.94	-2.99
Isopropylaniline (N-)	-0.26	-2.29	-3.33
Ketene	-1.92	-5.25	-6.54
Lindane	-2.26	-4.45	-5.62
Mesityl oxide	0.28	-0.59	-1.62
Methanol	1.49	-0.06	-1.10
Methoxychlor	-1.69	-4.92	-6.21
Methyl acetate	1.39	0.65	-0.27
Methyl acethylene	0.93	-0.22	-1.12
Methyl acrylate	-0.76	-1.58	-2.52
Methyl chloride	-0.30	-1.65	-2.56
Methyl chloroform	1.40	-0.62	-1.54
Methyl cyclohexane	1.32	-0.33	-1.26
Methyl cyclohexanone (o-)	0.88	0.12	-0.81

Methyl ethyl ketone (MEK)	1.39	0.39	-0.63
Methyl formate	0.55	-0.37	-1.31
Methyl iodide	-1.05	-2.80	-3.73
Methyl isoamyl ketone	0.36	-0.24	-1.20
Methyl isobutyl carbinol	0.54	-0.17	-1.19
Methyl isobutyl ketone	0.25	-0.27	-1.24
Methyl isopropyl ketone	0.30	-0.43	-1.42
Methyl mercaptan	-2.18	-3.02	-3.92
Methyl methacrylate	0.49	-0.04	-0.97
Methyl n-butyl ketone	-0.24	-0.88	-1.85
Methyl silicate	-0.78	-1.25	-2.20
Methyl tert-butyl ether (MTBE)	0.28	-0.85	-1.77
Methylacrylonitrile	-0.83	-1.52	-2.47
Methylal	1.94	0.96	0.02
Methylaniline (N-)	-0.77	-1.94	-2.97
Metribuzin	-1.05	-2.49	-3.55
Morpholine	0.53	-1.04	-2.02
Naphthalene	0.47	-0.30	-1.39
Neopentane	-0.08	-0.77	-1.67
Nicotine	-2.22	-4.33	-5.49
Nitrapyrin	-0.54	-2.57	-3.59
Nitroaniline (p-)	-1.05	-0.99	-1.96
Nitrobenzene	-0.80	-0.92	-1.92
Nitrochlorobenzene (p-)	-1.85	-2.24	-3.34
Nitroethane	1.09	0.64	-0.39
Nitroglycerin (NG)	-2.07	-4.07	-5.01
Nitromethane	0.43	-0.19	-1.25
Nitrotoluene (m-)	-0.51	-1.19	-2.24
Nitrotoluene (o-)	-0.52	-1.29	-2.35
Nitrotoluene (p-)	-0.50	-1.00	-2.05
Nonane	1.15	-0.48	-1.41
Octachloronaphthalene	-3.43	-6.94	-8.24
Oxybis(p,p'-)	-2.94	-4.43	-5.41
Paraquat	-3.28	-5.68	-6.90
Pentachloronaphthalene	-2.47	-4.95	-6.19
Pentachloronitrobenzene	-2.26	-4.28	-5.26
Pentachlorophenol	-2.56	-4.74	-5.91
Pentane	0.60	-0.42	-1.32
Perfluorobutyl ethylene	-1.64	-3.67	-4.59
Phenol	-0.16	-1.55	-2.66
Phenyl ether, vapor	-0.89	-2.06	-3.13
Phenyl glycidyl ether	-1.80	-2.55	-3.59
Phenyl mercaptan	-1.51	-3.46	-4.42
Phenylenediamine (m-)	-2.43	-3.02	-4.03
Phenylenediamine (o-)	-2.41	-2.23	-3.13
Phthalonitrile (o-)	-1.35	-2.11	-3.27
Picloram	-0.99	-3.04	-4.20
Pindone	-3.35	-5.73	-6.94
Propargyl alcohol	-0.80	-2.02	-3.06
Propyl nitrate (n-)	0.18	-0.42	-1.32
Propylene	-0.04	-1.15	-2.06
Propylene dichloride	-1.55	-1.22	-2.12
Propylene glycol dinitrate	-2.12	-2.24	-3.14
Propyleneimine	-1.20	-3.20	-4.26
Pyridine	-0.49	-2.16	-3.18
Quinone	-1.78	-1.50	-2.40
Rotenone	-1.99	-4.69	-5.96
Simazine	-2.07	-3.72	-4.72
Strychnine	-2.74	-3.22	-4.22
Styrene	0.73	-1.09	-2.06
Sulfometuron methyl	-1.24	-1.22	-2.12
Terephthalic acid	-0.87	-2.95	-4.11
Tetrachloroethylene	0.52	-1.35	-2.29
Tetrachloronaphthalene	-1.58	-3.73	-4.90
Tetrafluoroethylene	-3.37	-3.90	-4.80
Tetrahydrofuran	0.74	-0.75	-1.76
Tetramethyl succinonitrile	-1.09	-1.37	-2.40
Tetranitromethane	-3.13	-2.91	-3.81
Toluene	0.52	-1.00	-1.97
Toluidine (m-)	-0.19	-1.90	-2.89

Toluidine (o-)	-0.19	-1.89	-2.89
Toluidine (p-)	-0.17	-1.15	-2.20
Trichloronaphthalene	-0.86	-2.85	-3.90
Triethylamine	-0.91	-2.92	-3.88
Trifluorobromomethane	-0.58	-1.43	-2.34
Vinyl acetate	-0.36	-0.84	-1.74
Vinyl-2-pyrrolidone (N-)	-2.10	-3.21	-4.26
Vinylcyclohexene dioxide	-1.82	-3.31	-4.39
Vinylidene chloride	-0.83	-2.63	-3.55
Vinylidene fluoride	-0.73	-1.46	-2.36
Warfarin	-3.87	-3.52	-4.42
Xylene (m-)	1.38	-0.43	-1.39
Xylene (o-)	1.41	-0.59	-1.54
Xylene (p-)	1.37	-0.43	-1.39