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Par

Zohra CHUPEAU

Exposition aux retardateurs de flammes organophosphorés et neurodéveloppement de l'enfant

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Unité de recherche : INSERM U1085 – Institut de recherche en santé, environnement et travail (Irset)

Rapporteurs avant soutenance :

Isabelle Baldi PU-PH , Isped, Bordeaux
Jonathan Bernard Chargé de recherche, Inserm UMR 1153, Villejuif

Composition du Jury :

Président : Christophe Paris PU-PH, Faculté de Médecine, Rennes
Examineurs : Claire Philippat Chargée de recherche, Inserm UMR 1209, Grenoble
 Isabelle Baldi PU-PH , Isped, Bordeaux
 Jonathan Bernard Chargé de recherche, Inserm UMR 1153, Villejuif

Dir. de thèse : Philippe Glorennec Enseignant chercheur, Ecole des Hautes Etudes en Santé Publique, Rennes

Co-dir. de thèse : Cécile Chevrier Directrice de recherche, Inserm UMR 1085, Rennes

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Communications orales

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Chupeau, Z., Mercier, F., Rouxel, E., Le Bot, B., Chauvet, G., Siméon, T., Bonvallot, N., Zaros, C., Chevrier, C., Glorennec, P., Pre- and post-natal exposure of children to organophosphate flame retardants: a nationwide survey in France. Journée scientifique de l'école doctorale Biologie Santé , 9 et 10 décembre 2021, Rennes, France.

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Liste des abréviations

ANR : Agence Nationale de Recherche

BAS : British ability scale

BDE 209 : Polybrominated diphenyl ethers 209

BDE 47 : Polybrominated diphenyl ethers 47

COSV : Composés semi-volatiles

déca-BDE : Décabromodiphényléther

DOHaD : Developmental Origins of Health and Diseases

EHDPP : Ethylhexyldiphényl phosphate

GABA : Gamma aminobutyric

GHR : Groupes Homogènes de Réponses

HBCDD : Hexabromocyclododécane

IMC : Indice de masse corporelle

IP-PPP : Isopropylphenyle phenyl phosphate

KM : Kaplan-Meier

LOD : Limite de détection

logP : Coefficient de partage octanol/eau

MLE : Maximum de vraisemblance

octa-BDE : Octabromodiphényléther

PBB : Biphényles polybromés

PBDE : Diphényléthers polybromés

penta-BDE : Pentabromodiphényléther

POP : Polluants organiques persistants

PST : Picture Similarities test

REACH : Registration, Evaluation, Authorization and restriction of Chemicals

RF : Retardateurs de flamme

RFB : Retardateurs de flamme bromés

RFOP : Retardateurs de flamme organophosphorés

RFP : Retardateurs de flamme phosphorés

RoHS : Restriction of hazardous substances in electrical and electronic equipment

ROS : Robust regression on order statistics

TBBPA : Tétrabromobisphénol A

TBEP : Tris(2-butoxyethyl)phosphate

TCEP : Tris (2-chloroethyl) phosphate

TCPP : Tris(1-chloro-2-propyl)phosphate

TDCPP : Tris (1,3 -dichloroisopropyle)

TDN : Troubles du neurodéveloppement

TEP : Triethyl phosphate

TNBP (appelé aussi TBP) : Tris (butyl) phosphate

TPHP : Tris (phenyl) phosphate

UE : Union Européenn

Introduction

Les troubles du neurodéveloppement, aussi appelé TDN, touchent 10 à 15 % des enfants d'âge scolaire. Les TDN correspondent à un défaut de développement d'une ou plusieurs compétences cognitives attendues lors du développement psychomoteur et socio-affectif de l'enfant, qui entraîne un retentissement important sur le fonctionnement adaptatif scolaire, familial et social (Des Portes, 2020). Le neurodéveloppement inclut les capacités cognitives, mais aussi le comportement social et la maturité émotionnelle (Zhao et al., 2022). Une étude de l'assurance maladie a montré que 45 % des affections de longue durée des enfants de moins de 15 ans étaient des TDN. Plusieurs facteurs de risque de TDN ont déjà été identifiés comme la grande prématurité (moins de 32 semaines d'aménorrhée), un poids de naissance inférieur à 1 500 g ou encore l'exposition prénatale à un toxique majeur du neurodéveloppement (Des Portes, 2020). Ce dernier point illustre le concept DOHaD (Developmental Origins of Health and Diseases) présenté par le médecin David Barker dans les années 1980 qui suggère que les expositions du fœtus et de l'enfant au cours de ces premières années de vie à certains polluants peuvent avoir un impact à long terme sur le développement de l'organisme (Barker et al., 1989). Plus précisément, des expositions à des polluants au cours des fenêtres sensibles du développement du système nerveux, notamment lors de la prolifération et la différenciation des neurones, la migration cellulaire, la formation des synapses et la myélinisation, peuvent impacter le développement du cerveau et entraîner l'apparition de troubles neuropsychologiques au cours de la vie de l'individu. De nombreuses études ont ainsi mis en évidence des troubles du comportement et des déficits cognitifs et psychomoteurs chez des enfants exposés tôt dans la vie à de faibles niveaux de substances chimiques telles que le plomb (Bellinger, 2012, 2008), le mercure (Farías et al., 2022 ; Llop et al., 2012) et les insecticides organophosphorés (Inserm. Pesticides et effets sur la santé: Nouvelles données. Collection Expertise collective. Montrouge: EDP Sciences, 2021). Une forte prévalence de l'exposition à des neurotoxiques connus ou potentiels implique que les éventuels enjeux sociétaux, sanitaires et économiques sont majeurs (Bellinger, 2012). Un

règlement nommé Registration, Evaluation, Authorization and restriction of CHemicals (REACH) est entré en vigueur le 1^{er} juin 2007 pour encadrer l'utilisation des substances chimiques au sein de l'Union Européenne (UE). Son but est de protéger la santé humaine et l'environnement contre les risques liés aux substances chimiques, tout en favorisant la compétitivité de l'industrie chimique de l'UE. Cette réglementation implique l'évaluation des substances par les entreprises en amont de leur utilisation. Elles doivent démontrer que la substance peut être utilisée en toute sécurité, et communiquer les mesures de gestion des risques aux utilisateurs. Une des méthodes utilisées par les industriels pour évaluer la dangerosité d'une substance est l'essai sur les animaux. À l'issue de cette évaluation, les substances classées cancérigène, mutagène ou toxique pour la reproduction ou persistantes dans l'environnement sont progressivement remplacées. Cependant, les effets à long terme sur le neurodéveloppement humain des substances chimiques ne sont pas étudiés avant leur utilisation ("Comprendre REACH").

Il est donc nécessaire d'étudier leur potentiels effets neurotoxiques *a posteriori*. Si des mesures de prévention ont permis de réduire l'exposition à certaines substances dont les effets néfastes pour la santé ont été démontrés, les effets de produits chimiques de substitution ne sont toujours pas connus. C'est le cas notamment d'une catégorie de retardateurs de flamme appelés retardateurs de flamme organophosphorés (RFOP). Ces retardateurs ont des similitudes structurelles avec les pesticides organophosphorés, faisant ainsi craindre des effets neurotoxiques. Les retardateurs de flamme (RF), aussi appelés agents ignifuges, sont, depuis les années 1960, ajoutés par les industriels lors de la fabrication de produits de consommation variés (plastiques, textiles, équipements électriques et électroniques, etc.) afin de les rendre moins inflammables. Ces substances font partie de la grande famille chimique des composés semi-volatiles (COSV). Ils peuvent donc potentiellement être retrouvés dans les environnements intérieurs et extérieurs. Il existe 7 grandes familles de RF : les hydroxydes métalliques (ex : trihydroxyde d'aluminium, dihydroxyde de magnésium), les retardateurs de flamme phosphorés (RFP) incluant les RFOP, les retardateurs de flamme bromés (RFB), les

paraffines chlorées, les borates et les stannates, les trioxydes d'antimoine et les RF à base de mélamine (van der Veen and de Boer, 2012).

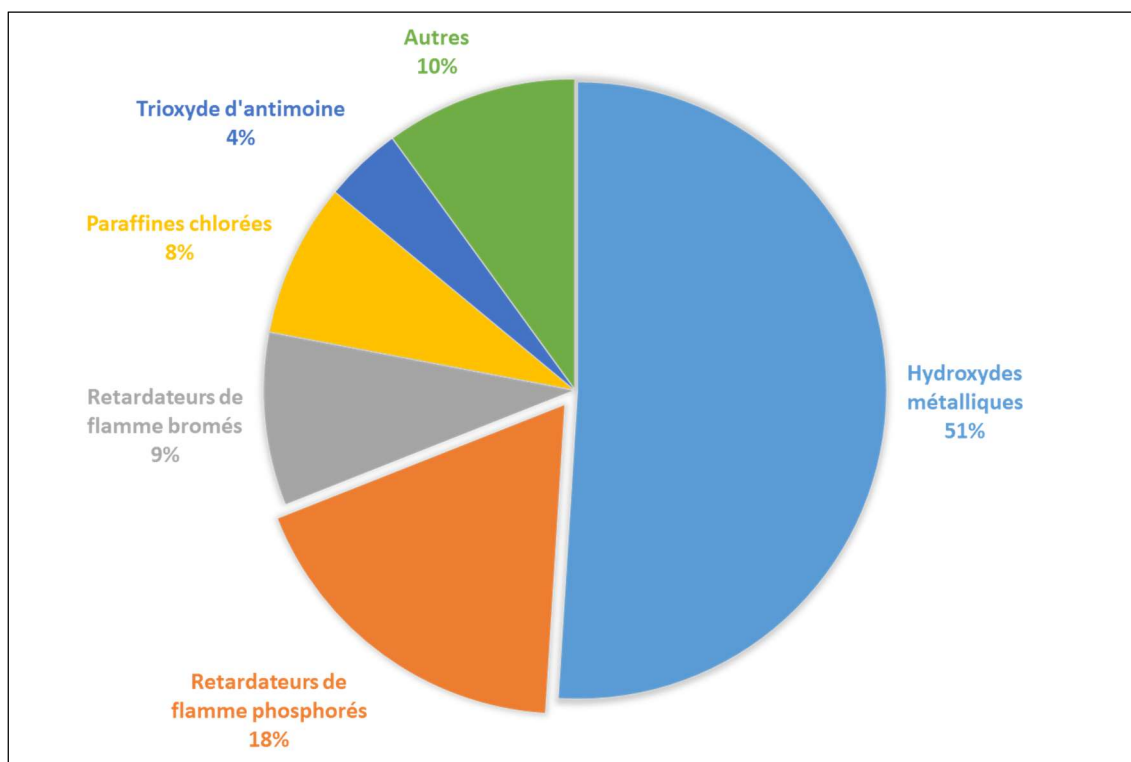


Figure 1. Estimation de la consommation totale de RF en Europe, en 2015 (Pinfa, 2017).

En Europe, en 2015, la consommation industrielle totale de RF était estimée à 498 000 tonnes dont 9 % étaient des RFB et 18 % des RFP (Pinfa, 2017). Il existe 5 catégories principales de RFB : les diphenyléthers polybromés (PBDE), l'hexabromocyclododécane (HBCDD), le tétrabromobisphénol A (TBBPA) et autres phénols, les biphenyles polybromés (PBB) et autres retardateurs de flamme bromés ("Retardateurs de flamme bromés"). Les PBDE ont été les plus étudiés en termes d'impacts négatifs sur la santé et l'environnement. A cause de leurs propriétés de bioaccumulation et de persistance dans l'environnement et le corps humain, ils ont été classés comme polluants organiques persistants (POP) par la convention de Stockholm¹. Leur utilisation est donc limitée depuis les années 2000. Ils ont donc été progressivement remplacés, notamment par des RFOP. Ces derniers ont été retrouvés dans

¹ Directive 2003/11/CE du parlement européen et du conseil du 6 février 2003 portant vingt-quatrième modification de la directive 76/769/CEE du Conseil relative à la limitation de la mise sur le marché et de l'emploi de certaines substances et préparations dangereuses (pentabromodiphényléther, octabromodiphényléther).

les environnements intérieurs (Chupeau et al., 2020) mais aussi chez l'Homme. En effet, des populations à risque, en particulier les enfants et les femmes enceintes peuvent être exposés aux RFOP par les aliments, mais aussi l'ingestion de poussières (de Boer et al., 2016), l'inhalation de l'air (Stapleton et al., 2009) ou le contact cutané avec l'air et la poussière (Abou-Elwafa Abdallah et al., 2016). Aux Etats-Unis, des métabolites de RFOP ont été détectés dans les urines de femmes enceintes (Castorina et al., 2017b ; Doherty et al., 2019 ; Hoffman et al., 2014). Au Japon et en Allemagne, ils ont été mesurés dans les urines prélevées chez les enfants (Araki et al., 2018). En Norvège, les RFOP ont aussi été mesurés dans les cheveux d'enfants et de mamans (Kucharska et al., 2015). Enfin, en Espagne, ils ont été mesurés dans le lait maternel (Beser et al., 2019). De plus, des études toxicologiques démontrent une neurotoxicité des RFOP comparable aux insecticides organophosphorés avec lesquels ils partagent une similarité structurelle (Patisaul et al., 2021). Cependant, aucune étude n'a été menée en France pour évaluer l'exposition de la population aux RFOP et la connaissance des effets de ces substances sur la santé humaine et, en particulier sur le neurodéveloppement, est encore très limitée.

Ce travail de thèse appartient au projet « Exposure & Neurotoxic Effects of FLAME Retardants » (Enflam') qui a débuté en janvier 2017. Il s'appuie sur la cohorte Elfe et est financé par l'Agence Nationale de Recherche (ANR). L'objectif de ce projet est de décrire l'exposition aux RFOP et de ses déterminants dans la population générale pour la première fois en France et d'étudier si l'exposition prénatale à des RFOP, pourrait être associée à des troubles neurodéveloppementaux de l'enfant. L'objectif de la thèse est, à partir des données de la cohorte Elfe et des mesures de RFOP générées dans le cadre du projet Enflam', de tester les hypothèses suivantes :

- L'utilisation des RFOP (en substitut aux PBDE) entraîne une exposition de la population générale, y compris des femmes enceintes et des enfants.
- L'exposition prénatale et postnatale des enfants aux RFOP a un effet néfaste sur le neurodéveloppement.

La première partie de ce manuscrit sur publication décrit un état de l'art de la contamination des environnements intérieurs et l'exposition humaine en Europe et les études épidémiologiques existantes ; cette revue est publiée dans *International Journal of Environmental Research and Public Health* (Chupeau et al., 2020). La seconde partie du manuscrit décrit, sous forme de publication dans *Environnement International* (Chupeau et al., 2022), l'exposition pré et post natale des enfants aux RFOP et ses déterminants dans la population générale, en France. La troisième partie présente les résultats de l'analyse de l'association entre les expositions prénatales aux RFOP et les performances cognitives non verbales de l'enfant. La partie 4 est consacrée à une discussion générale et d'une conclusion.

CHAPITRE 1 : État de l'art sur la contamination des environnements intérieurs et l'exposition humaine en Europe et les preuves épidémiologiques existantes

1. Contexte

1.1 Contexte

En Europe, la vente et l'utilisation des retardateurs de flamme sont soumise à diverses réglementations, dont REACH et RoHS. REACH impose aux entreprises européennes d'enregistrer auprès de l'ECHA (European Chemicals Agency) les substances chimiques vendues ou utilisées. RoHS, pour « Restriction of hazardous substances in electrical and electronic equipment », est une directive européenne (2002/95/CE²) visant à limiter l'utilisation de certaines substances dangereuses, dont les PBDE et les PBB, dans les équipements électriques et électroniques. RoHS impose que les concentrations maximales des PBDE et des PBB soient de 0.1 % par unité de poids de matériau homogène. Une autre directive européenne, la directive 2003/11/CE³, interdit la vente de deux mélanges commerciaux de PBDE, pentabromodiphényléther (penta-BDE) et de l'octabromodiphényléther (l'octa-BDE), à des concentrations supérieures à 0.1 % de masse. Depuis juillet 2006, suite à la directive RoHS, tous les nouveaux équipements électriques et électroniques ne peuvent plus contenir de PBB et de PBDE, quelle que soit leur concentration. En juillet 2008, un troisième mélange de PBDE, appelé décabromodiphényléther (déca-BDE), initialement exempté de restrictions, a également été interdit par la Cour de justice européenne ("Retardateurs de flamme bromés"). En 2009, le Programme des Nations Unies de l'Environnement a décidé lors d'une réunion des différentes parties de la Convention de Stockholm (directive 2003/11/CE) de labelliser officiellement les mélanges commerciaux penta-BDE et octa-BDE comme POP (van der Veen and de Boer, 2012). Tous ces éléments ont conduit au développement et à l'utilisation croissante en particulier depuis les années 2000 d'alternatifs aux retardateurs de flamme bromés, dont les RFOP.

² Directive 2002/95/ce du parlement européen et du conseil du 27 janvier 2003 relative à la limitation de l'utilisation de certaines substances dangereuses dans les équipements électriques et électroniques.

³ Directive 2003/11/ce du parlement européen et du conseil du 6 février 2003 portant vingt-quatrième modification de la directive 76/769/CEE du Conseil relative à la limitation de la mise sur le marché et de l'emploi de certaines substances et préparations dangereuses (pentabromodiphényléther, octabromodiphényléther).

Les RFP peuvent être organiques ou inorganiques. Dans ce travail de thèse, nous nous intéressons plus spécifiquement aux RFP organiques (RFOP). Les RFOP incluent : les organophosphates, les organophosphonates, les organophosphinates, les oxydes d'organophosphine et les organophosphites (figure 2).

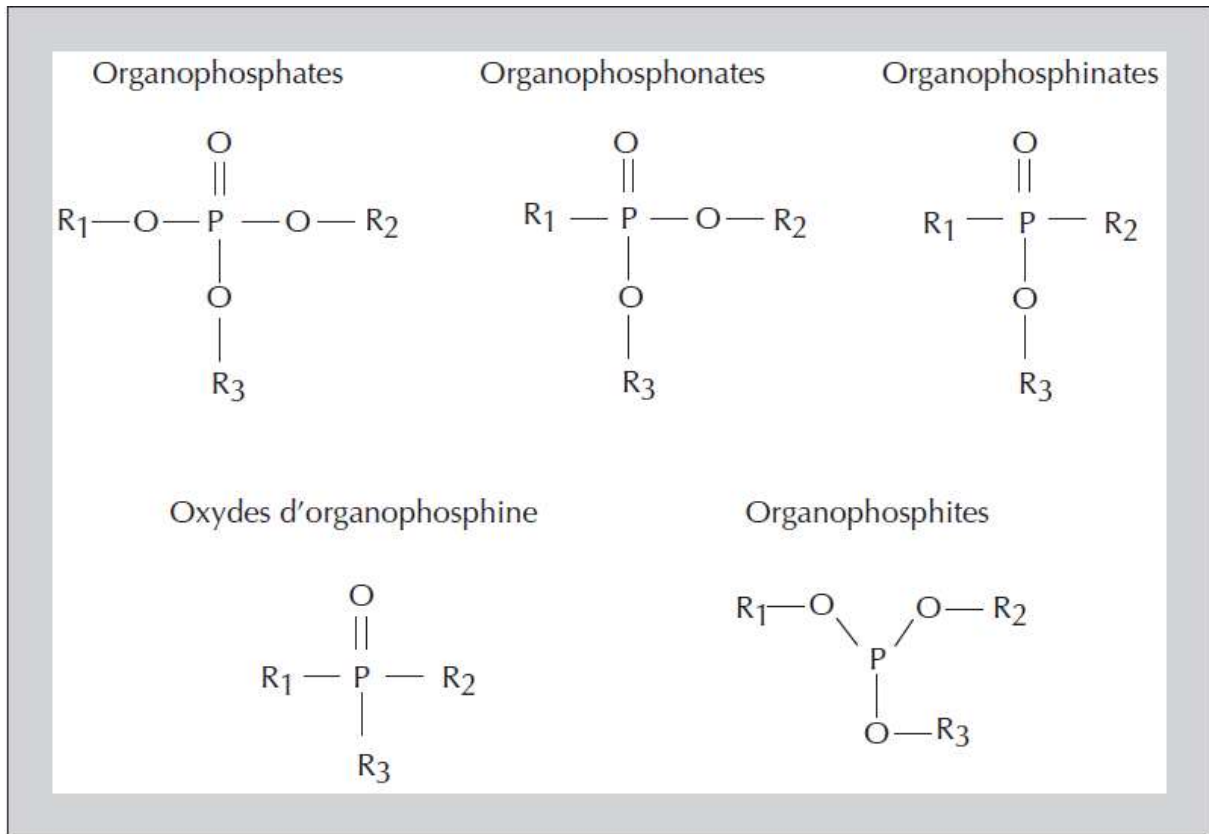


Figure 2. Structure chimique générales des retardateurs de flamme organophosphorés (Niang et al., 2019).

R_1 , R_2 et R_3 sont des substitués organiques. Ils peuvent être identiques ou différents. Un substitut organique est un atome ou un groupe d'atomes qui remplace un ou plusieurs atomes d'hydrogène sur la chaîne principale d'un hydrocarbure.

Les RFOP peuvent contenir un atome de chlore, ils sont donc dits « halogénés ». Ils combinent les propriétés des composés halogénés et phosphorés. La présence d'un halogène augmente la durée de vie du retardateur de flamme dans le produit final en diminuant sa mobilité dans le polymère. Le tris (2-chloroethyl) phosphate (TCEP) ou le tris(1-chloro-2-propyl) phosphate (TCPP) sont des exemples de RFOP halogénés. Les RFOP halogénés sont en majorité des

phosphinates. Le TCPP représente approximativement 80 % des RFP chlorés en Europe et c'est le RFP le plus utilisé en Europe (en volume) au début des années 2000 (van der Veen and de Boer, 2012).

Les RFOP sont utilisés en tant qu'additifs. Ils sont seulement mélangés au polymère, mais ne sont pas liés chimiquement à ce dernier. Cette absence de liaison chimique peut entraîner un rejet du RFOP dans l'environnement par abrasion et volatilisation (Kucharska et al., 2015).

Différentes propriétés physico-chimiques caractérisent les RFOP dont : la solubilité dans l'eau, la masse moléculaire, la lipophilie (vs l'hydrophilie) mesurée par le logarithme de coefficient de partage octanol/eau (logP), la dissolution du gaz dans un liquide mesurée par la loi de Henry, l'accumulation par les organismes aquatiques de substances à une concentration supérieure à celle mesurée dans l'eau, le facteur de bioaccumulation, le point d'ébullition, le point de fusion et le point d'inflammabilité correspondant à la température la plus basse à laquelle un corps combustible émet suffisamment de vapeur pour former dans l'air un mélange gazeux qui s'enflamme sous l'effet d'une source de feu. La solubilité diminue quand la masse moléculaire augmente. Beaucoup de RFOP ont un logP positif signifiant qu'ils sont davantage lipophiles que hydrophiles. Concernant le facteur de bioaccumulation, celui-ci augmente avec la masse moléculaire excepté pour les molécules contenant du chlore. Ainsi, les RFOP non halogénés avec une masse moléculaire élevée peuvent être davantage retrouvés dans la nature que les RFOP avec une masse moléculaire plus faible (van der Veen and de Boer, 2012).

Lors d'un incendie, la combustion des matériaux de type polymère organique se décompose en deux étapes. La première étape consiste en la décomposition thermique du polymère par échauffement de ce dernier entraînant la libération de liquide, de solides, de gaz non combustibles, mais aussi de gaz combustibles. La seconde étape consiste en l'oxydation des gaz combustibles par un comburant qui est généralement l'oxygène de l'air. Ce sont ces réactions d'oxydo-réduction du couple combustible/comburant qui constitue la flamme. Ainsi,

la combustion d'un matériau ne concerne pas le matériau solide lui-même, mais les gaz inflammables qui s'en échappent (Negrell and Ménard, 2016).

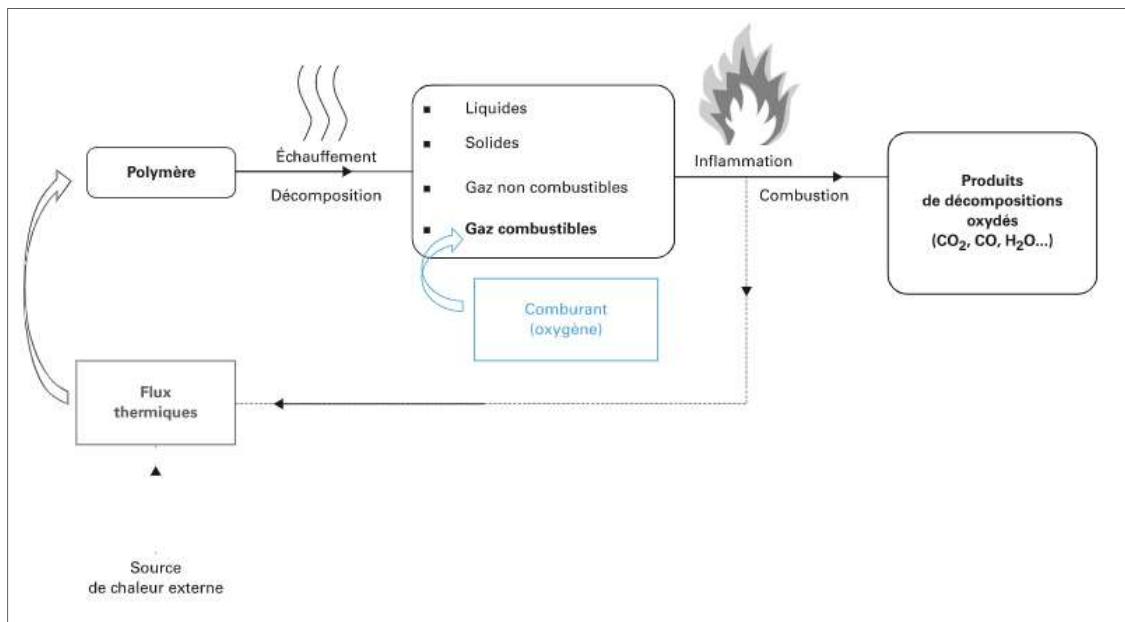
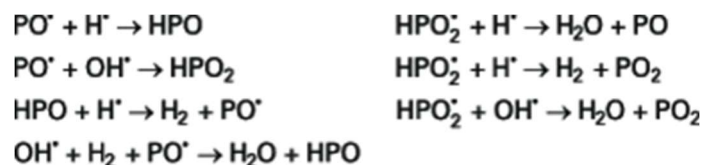


Figure 3. Procédé de combustion (C. Negrell, R. Ménard, Retardateurs de flamme phosphorés commerciaux pour les polymères, réf. AF6047, Techniques de l'Ingénieur (2016)).

Les retardateurs de flamme peuvent avoir une action physique et/ou une action chimique. Lors d'une action chimique, les retardateurs de flamme peuvent agir en phase gazeuse ou en phase condensée (ou solide). Les RF phosphorés présentent l'avantage de combiner ces deux modes d'action. Plus l'atome de phosphore du RF est oxydé plus le RF est efficace en phase condensée. Ainsi, les RF de type « phosphine » sont les plus efficaces en phase gazeuse alors que les composés de type « phosphate » sont les plus efficaces en phase condensée. En phase gazeuse, le processus de combustion est chimiquement interrompu par le RF. En effet, les radicaux phosphorés issus de la dégradation thermique du RF de type PO° captent les radicaux hydrogènes dits « chauds » de la flamme qui sont de type H° et OH° . L'élimination des radicaux H° et OH° entraîne un ralentissement du processus de combustion et réduit la propagation de l'incendie. Ce phénomène est appelé « Inhibition de flamme » (Negrell and Ménard, 2016).



Puis, en phase condensée, lorsque le phosphore est chauffé, il réagit et apparaît une forme polymérique d'acide phosphorique. Cet acide forme une couche de charbon (appelé char) qui protège le matériau de l'oxygène (effet barrière), empêchant ainsi la formation de gaz inflammables (van der Veen and de Boer, 2012).

Enfin, lors de l'action physique, se forme une couche de barrière isolant la phase condensée de la source de chaleur et limitant ainsi le transfert des gaz combustibles vers la flamme. C'est ce que l'on appelle le phénomène d'intumescence.

La figure ci-dessous résume l'action des retardateurs de flamme phosphorés en présence d'un incendie.

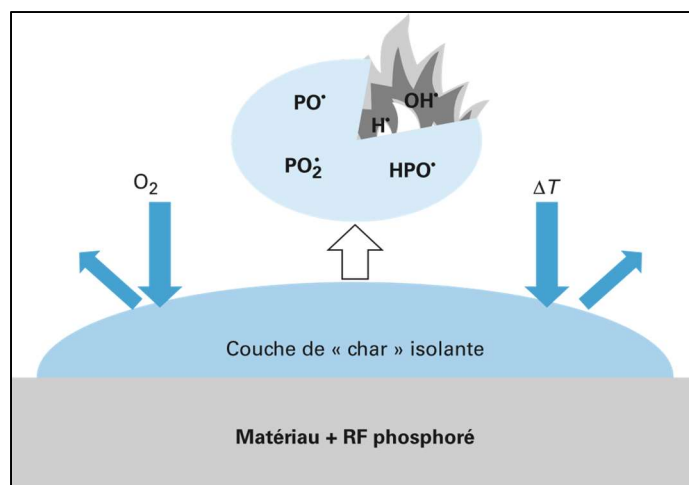


Figure 4. Action des retardateurs de flamme phosphorés lors d'un incendie (C. Negrell, R. Ménard, Retardateurs de flamme phosphorés commerciaux pour les polymères, réf. AF6047, Techniques de l'Ingénieur (2016)).

Les RFOP n'étant pas liés chimiquement au matériau final, ils peuvent donc être relargués dans l'environnement. Certains ont été retrouvés dans les rivières (ex : TPHP), les sédiments (ex : TCPP) ainsi que la biota (ex : TCEP). Ils s'introduisent ensuite dans la chaîne alimentaire et peuvent contaminer l'Homme (van der Veen and de Boer, 2012).

Une analyse détaillée des données existantes depuis 2000 en Europe sur la présence de RFOP dans les environnements intérieurs et l'exposition des populations à ces substances a été réalisée, accompagnée d'un état de l'art des données épidémiologiques disponibles étudiant un rôle possible de ces substances sur la santé humaine. Les résultats de ces recherches sont présentés dans un article intitulé « *Organophosphorus Flame retardants : A Global Review of Indoor Contamination and Human Exposure in Europe and Epidemiological Evidence* » (Chupeau et al., 2020).

1.2 Etat de l'art sur les RFOP

Un état de l'art a été réalisé pour identifier les RFOP les plus préoccupants afin d'orienter les futures recherches et les actions à mener. Nous nous sommes intéressés à la littérature publiée entre 2000 et 2019 sur la présence des RFOP dans les environnements intérieurs et dans les matrices biologiques humaines en Europe ainsi que sur les preuves épidémiologiques existantes. Le choix réaliser la revue de littérature seulement sur les données européennes pour la contamination des environnements intérieurs et l'exposition humaine s'explique par la présence d'une réglementation commune à tous les pays de l'UE (REACH) sur l'utilisation des substances chimiques. Les années 2000 étant le début de l'interdiction des PBDE qui seront progressivement remplacés par les RFOP, nous avons choisi de nous intéresser à la littérature publiée après cette date. Nous avons également choisi de ne sélectionner que les études dont le nombre d'échantillons (d'air, de poussières, de matrices biologiques) étaient supérieurs ou égale à 10. Les RFOP les plus concentrés dans les poussières étaient le TBEP, le TCPP et le TDCPP, et dans l'air, le TCPP et le tris (butyl) phosphate (TNBP). Parmi ces RFOP, le TBEP et le TCPP se sont également avérés avoir les concentrations les plus élevées dans les matrices humaines (urine, cheveux, lait maternel), en particulier chez les enfants. Le TDCPP et le TNBP ont également été mesurés dans les matrices humaines, mais en concentrations plus faibles. Le TDCPP est l'un des RFOP le plus étudié dans les études épidémiologiques. Il est associé à de multiples effets néfastes sur la santé incluant des effets sur le système reproducteur (diminution de la qualité spermatique (Meeker et al., 2013) , sur la thyroïde

(modification de la concentration sanguine des hormones thyroïdienne T3 et thyroïdostimuline (TSH) (Meeker et al., 2013), T4 libre (Meeker and Stapleton, 2010)) , sur la capacité d'attention chez les enfants (Castorina et al., 2017a), sur le système respiratoire (respiration sifflante (Ait Bamai et al., 2018),rhino-conjonctivite (Araki et al., 2018)) et sur la peau (eczema ((Araki et al., 2018)). Ce RFOP semble être particulièrement préoccupant en raison d'une forte prévalence d'exposition et de preuves épidémiologiques. Bien que le TBEP et le TNBP ont été fréquemment mesurés dans les environnements intérieurs et les matrices humaines, les études épidémiologiques se sont principalement intéressées à leurs effets possibles sur le système respiratoire. D'autres études épidémiologiques seraient nécessaires pour ces deux composés. Enfin, nous avons constaté un manque de données concernant les concentrations d'Isopropylphényle phényl phosphate (IP-PPP) dans les environnements intérieurs et les matrices humaines en Europe. De plus, l'IP-PPP a été classé comme potentiellement neurotoxique et reprotoxique pour le fœtus (Département de la Santé du Vermont) ; pouvant inciter à la réalisation d'autres études épidémiologiques avec une puissance statistique suffisante pour évaluer l'impact sur le neurodéveloppement. De manière plus générale, les effets sur le neurodéveloppement semblent avoir été moins étudiés que d'autres effets sur la santé et méritent une attention particulière.



Review

Organophosphorus Flame Retardants: A Global Review of Indoor Contamination and Human Exposure in Europe and Epidemiological Evidence

Zohra Chupeau^{1,2}, Nathalie Bonvalot^{2,3}, Fabien Mercier^{2,3} , Barbara Le Bot^{2,3},
Cecile Chevrier^{1,2} and Philippe Glorennec^{2,3,*}

¹ INSERM—Institut National de la Santé et de la Recherche Médicale, F-75000 Paris, France; zohra.chupeau@univ-rennes1.fr (Z.C.); cecile.chevrier@univ-rennes1.fr (C.C.)

² IRSET—Institut de Recherche en Santé, Environnement et Travail, UMR1085, F-35000 Rennes, France; Nathalie.Bonvalot@ehesp.fr (N.B.); Fabien.Mercier@ehesp.fr (F.M.); barbara.lebot@ehesp.fr (B.L.B.)

³ EHESP—Ecole des Hautes Etudes en Santé Publique, F-35000 Rennes, France

* Correspondence: philippe.glorennec@ehesp.fr

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Abstract: We aimed to identify high-priority organophosphorus flame retardants for action and research. We thus critically reviewed literature between 2000 and 2019 investigating organophosphorus flame retardants' presence indoors and human exposure in Europe, as well as epidemiological evidence of human effects. The most concentrated compounds indoors were tris(2-butoxyethyl)phosphate (TBOEP), tris(1-chloro-2-propyl)phosphate (TCIPP), tris(2,3-dichloropropyl)phosphate (TDCIPP). TBOEP and TCIPP were the most consistently detected compounds in humans' urine, hair or breast milk as well as tris (butyl) phosphate (TNBP) and tris (phenyl) phosphate (TPHP). Notably, epidemiological evidence concerned reprotoxicity, neurotoxicity, respiratory effects and eczema risk for TDCIPP, eczema increase for TBOEP, and neurodevelopmental outcomes for Isopropylated triarylphosphate isomers (ITPs). Given the ubiquitous presence indoors and the prevalence of exposure, the growing health concern seems justified. TDCIPP and TPHP seem to be of particular concern due to a high prevalence of exposure and epidemiological evidence. TBOEP and TNBP require epidemiological studies regarding outcomes other than respiratory or dermal ones.

Keywords: environmental health; indoor air quality; epidemiology; biomonitoring; chemical safety; organophosphate ester

1. Introduction

Flame retardants are chemical compounds that have, since the 1960s, been added to many products during the manufacturing process [1] with the intention of minimizing the risk of a fire starting, or reducing fire propagation [2]. Polybrominated biphenyls were used in products until they were phased out in 1976. They were replaced by a very similar set of chemicals called polybrominated diphenyl ethers, a family of brominated flame retardants. Polybrominated diphenyl ethers were the most commonly used flame retardants until the early 2000s [3]. They were added to consumer products, including furniture, children's products, and electronics [4]. Because of their negative impacts on both the environment and health, due to their bioaccumulation and persistence properties, they have been classified as persistent organic pollutants (POPs) under the Stockholm Convention and their use has been restricted in Europe since the 2000s [5–8]. Organophosphorus Flame Retardants (OPFRs) were used, among their other uses as plasticizers or lubricants, as a replacement for brominated flame retardants to maintain fire safety standards after their phase-out [9,10]. In Europe, the total consumption of flame retardants in 2015 was 498,000 metric

tons, of which 18% were phosphorus flame retardants, representing 89,640 metric tons [11]—twice as much as brominated flame retardants. OPFRs are the second-largest flame retardants used in Europe, after aluminum trihydroxide [11]. OPFRs are organic esters of phosphoric acid, containing ether alkyl chains or aryl groups, and may be halogenated or nonhalogenated [4]. Halogenated organophosphates are used as flame retardants, while nonhalogenated organophosphates are mostly used as plasticizers in consumer products, textiles and construction materials [12,13]. More specifically, halogenated organophosphates containing such chlorinated forms as tris(1-chloro-2-propyl)phosphate (TCIPP) or tris(2,3-dichloropropyl)phosphate (TDCIPP) are also widely used in furniture, textiles, building materials, polyurethane foam and electronics. Nonhalogenated flame retardants such as tris(2-butoxyethyl)phosphate (TBOEP), Trimethylphosphate (TMP) or Tris(3,5-xilylenyl)phosphate (TXP) are mostly used in floor polishes, coatings, engineering thermoplastics and epoxy resins [10]. All OPFR acronyms used are presented in Table S1.

OPFRs are not chemically bound in products and may release into the environment via volatilization, leaching and/or abrasion [14]. They are ubiquitous in the environment and, since the early 2000s, can be found in water, biota, sediment and soil; because of their widespread use in consumer products, they are especially present in indoor environments in which they partition air and dust [15]. OPFRs have thus the potential to expose a population via the ingestion of dust, inhalation of air or dermal contact with both.

Toxicological studies have observed hazards including neurotoxic and endocrine effects. TMP and tris (phenyl) phosphate (TPHP) are estrogen receptor agonists [16]. Furthermore, several OPFRs (TPHP, TMP, Ethylhexyldiphényl phosphate (EHDPP), Tri-*o*-cresylphosphate (ToCP), Isodecyl diphenyl phosphate (IDPP), TDCIPP, and Tris(2-chloroethyl)phosphate (TCEP)) have induced a reduction in the proliferation and growth of human neural stem cells, rat neuronal growth and network activity [17].

Considering current use and human health concerns, with increasing numbers of studies being dedicated to OPFRs, several reviews have already been performed. Although these have focused on just one or two aspects (such as contamination, exposure or health effects), it remains important to consider all aspects in order to characterize the public health concern. As regulations differ from one country or group of countries to another, we focused on Europe with the perspective of identifying compounds of concern for (bio)monitoring or regulation.

We reviewed the literature with the following objectives: (i) to identify the compounds of greatest concern in Europe regarding indoor contamination, human exposure and epidemiological evidence and (ii) to identify priority data gaps in knowledge. We therefore reviewed recent European studies dedicated to indoor contaminations and exposures. Because health hazards are not location-specific, we reviewed the epidemiological evidence without geographic restriction.

2. Materials and Methods

The search covered the period from 2000 to 2019. This review has compiled OPFR concentrations of indoor air and dust in Europe, human intake in Europe, human exposure in Europe, and epidemiological studies worldwide regardless of location, given the expected low variability in human response. Because the review is ultimately interested in human health, the search was conducted in the PubMed database using the request: organophosphorus flame retardant*[Title/Abstract] OR OPFR[Title/Abstract] OR phosphorus flame retardant*[Title/Abstract] OR phosphate ester flame retardant*[Title/Abstract] OR organophosphate flame[Title/Abstract] OR phosphate flame retardant*[Title/Abstract] OR organophosphate ester flame retardant*[Title/Abstract] OR organophosphate triester*[Title/Abstract] OR organophosphate ester*[Title/Abstract] OR organic flame retardant*[Title/Abstract] OR PFR*[Title/Abstract] OR OPE*[Title/Abstract] OR phosphate triester flame retardant*[Title/Abstract]. A total of 2037 articles were identified and sorted by a single reviewer. Articles that did not match with the review subject or written in a language other than English were excluded on the basis of the title and abstract. Fifty-two articles were selected and classified according to their subject in five categories: “indoor air concentrations”, “indoor dust concentrations”,

“human intake estimations”, “biological measurements” and “epidemiological studies”. With the exception of studies on intake estimations, only studies with at least ten measurements were included, to ensure minimal representativeness.

Regarding publications about indoor air and dust concentration, the following items were retrieved: sampling conditions (country, period and location), sample size, minimal, maximal, mean and median concentrations and references. OPFRs’ median concentrations were compared between studies regardless of collection method. Regarding human intake, this review summarizes and compares the intake (or external doses) estimations of several OPFRs via various pathways (ingestion, dermal absorption and inhalation). Regarding publications on biological measurements, the following items were retrieved: metabolite name, parent compound(s), sampling conditions (country, population, size and year), minimum, maximum, mean and median concentrations and references. Regarding epidemiological studies, the following items were retrieved: country, population, and exposure assessment, compounds of interest, health outcomes observed, covariates and human health findings. Studies reporting only a correlation without assessing adjusted association between risk factors and health outcomes were not included.

3. Results and Discussion

3.1. Indoor Contamination

Thirty-one studies dealing with the contamination of indoor dust and/or air were identified and reviewed. OPFR concentrations with at least ten measurements were investigated in Belgium, the Czech Republic, Denmark, Germany, Norway, Romania, Spain, the Netherlands and the United Kingdom. We noticed that all studies used samples which were collected after 2006. Five studies collected more than 60 samples. In Denmark, Langer et al. (2016) [18] collected 497 dust samples from homes and 151 from daycare centers. Bergh et al. studied 169 air samples in Swedish homes [19]. Luongo and Östman (2016) [20] collected 62 dust and air samples from homes in Sweden, Fromme et al. (2014) [21] collected 63 air samples from German daycare centers and Xu [22] collected 61 air and dust samples from homes in Norway.

3.1.1. Dust

A total of 20 studies dealt with the contamination of indoor dust [18–21,23–38]. They are described in detail in the supplemental information (Table S2). Twenty-nine OPFRs were measured, and 26 were detected in the indoor dust of daycare centers, cars, private homes, offices and schools. The median dust concentration of compounds ranged from <0.0018 $\mu\text{g/g}$ in homes in the United Kingdom [33] to 1600 $\mu\text{g/g}$ in Swedish daycare centers [19]. Concentrations (for detected compounds) are shown in Figure 1. The ten OPFRs having the highest median concentration, independently of the considered indoor environment, were: TBOEP (median = 1600 $\mu\text{g/g}$ in day care centers in Sweden) > TCIPP (median = 65 $\mu\text{g/g}$ in UK homes) > TDCIPP (median = 31 $\mu\text{g/g}$ in UK cars) > TCEP (median = 30 $\mu\text{g/g}$ in homes in Sweden) > EHDPP (median = 29 $\mu\text{g/g}$ in UK classrooms) > TPHP (median = 9.79 $\mu\text{g/g}$ in homes in the Netherlands) > tris (butyl) phosphate (TNBP) (median = 5.60 $\mu\text{g/g}$ in homes in Sweden) > Tri-iso-butylphosphate (TIBP) (median = 5.3 $\mu\text{g/g}$ in homes in Sweden) > Tricresylphosphate (TMPP) (median = 2.7 $\mu\text{g/g}$ in homes in Sweden) > TPHP (median = 2.58 $\mu\text{g/g}$ in homes in The Netherlands).

The paragraph hereafter focuses with more details on studies published since 2012 and not included in the previous review by Wei [39]. The highest OPFR median concentrations were observed in Germany, the UK, Denmark and Sweden. However, the differences between countries may be related to the sample location (daycare centers, cars, private homes, offices and schools). For instance, the higher sum of OPFR concentrations observed in Sweden was explained by a particularly high median concentration of TBOEP in daycare centers (median = 1600 $\mu\text{g/g}$ [19]). The recent studies in homes were conducted in the UK, Sweden, Norway, the Netherlands, Denmark, Germany, the Czech Republic, Spain and Portugal. Almost the same OPFRs were analyzed in the UK, Sweden,

Norway, the Netherlands, Germany and the Czech Republic, although OPFR concentrations were different. In the UK, TCIPP was the most predominant compound, followed by TBOEP, whereas in Norway and Germany TBOEP was the most predominant compound, followed by TCIPP. In Sweden, TBOEP and TCIPP were the two OPFRs having the highest concentration. In the Czech Republic, TCIPP was the predominant but TBOEP was not analyzed. OPFR concentrations were higher in the UK and Sweden than in other countries, with a median concentration of total OPFRs (with different OPFRs between studies) of 49 µg/g in Sweden [20], 79 µg/g [33] and 27.44 µg/g [26] in the UK. TBOEP was the most predominant compound in daycare centers studied in Germany and Denmark, with a median concentration 8.5 times higher in Germany. In Denmark, the TBOEP median concentration was followed by the TCEP, TDCIPP and TCIPP median concentrations, while in Germany other OPFRs made a minor contribution (with TDCIPP not measured). Office samples were collected in the UK and Germany, and TCIPP was the most predominant in both countries. It was followed by TBOEP in Germany (not measured in the UK) and EHDPP in the UK. The EHDPP concentration was ten times higher in the UK than in Germany (median = 1.6 µg/g vs. median = 0.14 µg/g) [26,31]. The sum of the OPFR median concentration in the UK was higher than in Germany, mainly because of the high TCIPP concentration. School samples were collected in elementary all-day Austrian schools—only TCEP was measured, with a median concentration of 2.5 µg/g [32]. Samples were collected from cars in the UK, Germany and Spain. OPFR concentrations in the UK were nine times higher than in Germany, and 15 times higher than in Spain. OPFR profiles between the UK and Germany were similar, with TCIPP making a major contribution, followed by TDCIPP and TPHP [26,31]. Two OPFRs were measured in Spain: TPHP and DPHP. Only TPHP was measured in all three countries.

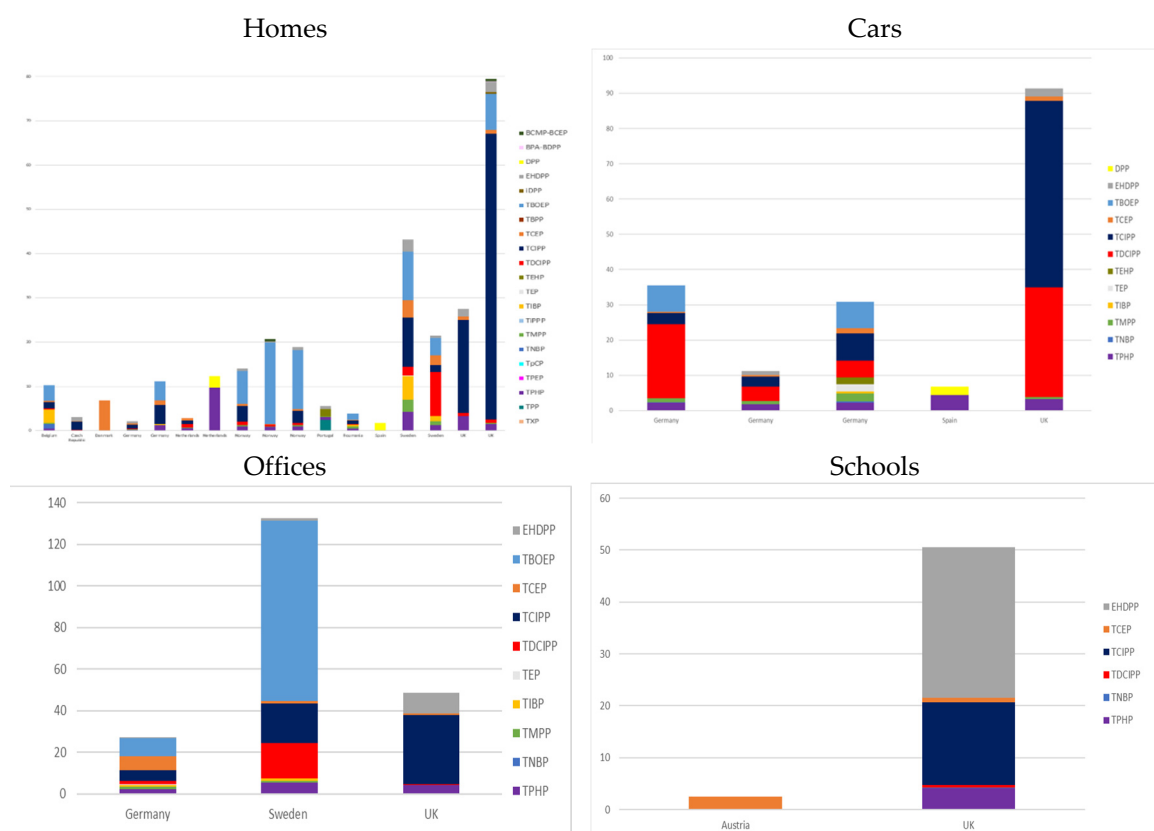


Figure 1. Cont.

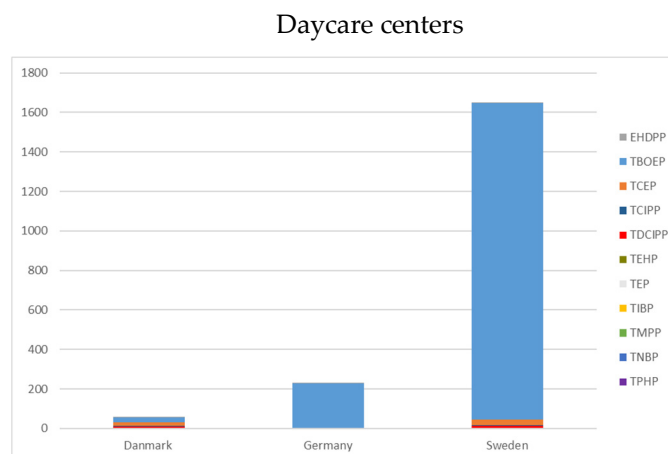


Figure 1. Organophosphorus Flame Retardants (OPFRs) dust median concentration in Europe, 2008–2018 ($\mu\text{g/g}$).

To conclude on OPFRs in dust, TBOEP, TCIPP and TDCIPP were the most concentrated in Europe. In homes, offices and cars, the predominant compound was TCIPP, whereas in daycare centers it was TBOEP. TDCIPP was found to be much higher in dust from vehicles and offices than in dust from the main living areas. These findings confirm those of previous review by Wei [39], who also mentioned high concentrations of TBOEP in home dust in non-European countries such as Japan. In addition, this update highlights that, in a given environment, OPFR concentrations in dust tend to be higher in the UK than in the rest of Europe, likely in line with more stringent fire safety regulations in the UK.

3.1.2. Air

A total of 10 studies [19–21,27,36,37,40–43] dealt with the contamination of indoor air in Europe and are presented in detail in Table S3. A total of 16 OPFRs were detected; median concentrations ranged from 0.001 ng/m^3 in homes in the Czech Republic [36] to 330 ng/m^3 in offices in Sweden [41]. However, the passive sampling technique (polyurethane foam) used by Vykoukalová may underestimate air concentrations by sampling, principally, the gas phase, contrary to other studies with active sampling. The five OPFRs with the highest median concentrations were: TCIPP (median = 330 ng/m^3 in offices in Sweden) > TNBP (median = 49 ng/m^3 in Germany daycare centers) > TDCIPP (median = 28 ng/m^3 in offices in Sweden) > TCEP (median = 25 ng/m^3 in daycare centers in Sweden) > TIBP (median = 13 ng/m^3 in homes in Sweden).

We describe hereafter the most recent (>2012) publications investigating indoor air contamination since the previous review by Wei [39], and have thus not included this in our investigation. In homes, air concentrations were measured in four countries: Sweden, Norway, the Czech Republic and Belgium. The concentrations of detected compounds are displayed in Figure 2. With the exception of Belgium (all median < LOD), countries had similar concentration profiles with a predominance of TCIPP followed by TNBP. However, the median TCIPP concentration was between 2 and 10 times higher in Norway than in Sweden or the Czech Republic. In daycare centers (Figure 2), TNBP and TCIPP were measured only in Germany, with TNBP being 25 times more concentrated than TCIPP. In offices (Figure 2), TCIPP largely predominates in Sweden and Germany, with median concentrations being 10 times higher in Sweden. Samples from schools were collected in Germany and Sweden (Figure 2). In Germany, TCIPP, TNBP and TIBP were measured with a similar contribution of TCIPP and TNBP, while in Sweden, only TPHP was analyzed. No study was found that included air sample measurements from cars.

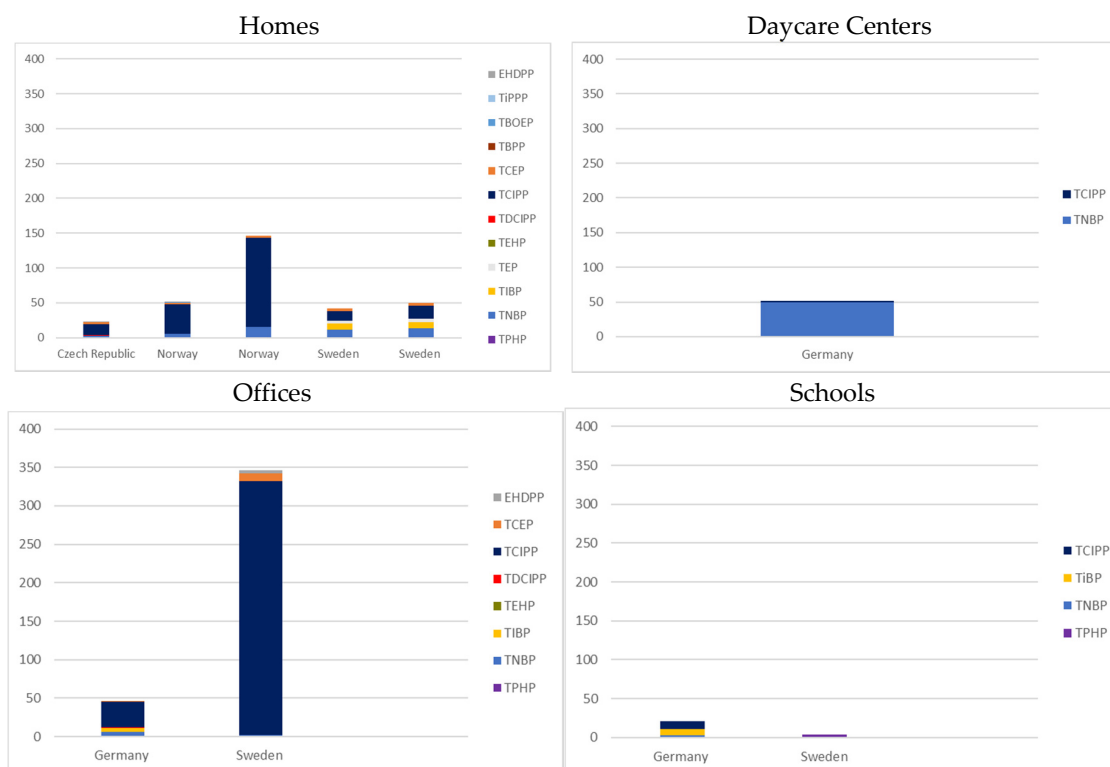


Figure 2. OPFRs air median concentration in Europe, 2000–2018 (ng/m^3) (one bar per article).

To conclude on European indoor air, the two predominant compounds in air were TCIPP and TNBP, thus confirming previous findings from Wei, who noticed it was not specific to Europe [39]. TCIPP dominated in homes and offices, followed by TNBP, whereas in German daycare centers TNBP concentrations were higher than those of TCIPP.

Overall, on indoor air and dust contamination, 16 OPFRs were measured in air and 30 in dust. We should note that a comparison between all of these studies might be limited by possible heterogeneity in the detection limits and analytical protocols. We did not consider these elements in detail in this review and assume that among the most recent studies in Europe technical heterogeneities are likely to be small and only slightly influential on the present conclusions. The number of collected samples, the measured compounds and the sampling might also differ between studies. Globally, TBOEP and TDCIPP were more concentrated in dust than in air, in line with their log K_{oa} (13.1 and 10.6, respectively). Conversely, TNBP was present in air with a log K_{oa} of 8.2. TCIPP also has a log K_{oa} of 8.2 and was measured at a high concentration in both indoor matrices. Considering the findings, it would be useful to document more broadly the presence of, at least, these main OPFRs in air and dust of living spaces in Europe, considering more countries, and ideally on representative samples of homes, schools, an daycare centers.

3.2. Human Exposure to OPFRs in Europe

3.2.1. Intake Estimation

Because of the frequent occurrence of OPFRs in dust and air, humans are exposed to these pollutants via dust ingestion, dermal contact and inhalation, in addition to dietary intake [39]. Several studies have estimated OPFR intake using a similar concentration in the environment, ingestion rates and time-activity patterns [39].

Dust ingestion has long been considered the most important pathway for OPFR exposure [44,45]. The median ingestion via dust to the sum of OPFRs was estimated at 6.6 ng/kg bw/d for nonworking adults and 128 ng/kg bw/d for children in Belgium [46], at 6.5 ng/kg bw/d for adults and 22.4 ng/kg

bw/d for children in Germany [25], at 2.6 ng/kg bw/d for adults and 60.6 ng/kg bw/d for children living in urban areas in Romania [30], and at 8.9 ng/kg bw/d for adults in Norway [37]. Sums of OPFRs inform on global intake; however, comparisons are limited because the included compounds may differ from one study to another. Considering compounds separately, a 2015 study by Brommer and Harrad [26] on the UK population, estimated dust ingestion intake at 0.92 ng/kg bw/d for TCIPP, 0.07 ng/kg bw/d for TDCIPP and 0.03 ng/kg bw/d for TCEP in adults. With a higher frequency of hand-to-mouth behavior in children, Brommer and Harrad (2015) [26] estimated exposure via dust ingestion at 43 ng/kg bw/d for TCIPP, 4 ng/kg bw/d for TDCIPP and 1.7 ng/kg bw/d for TCEP in the UK. Therefore, toddler OPFR intake via dust ingestion was approximately 10 to 20 times higher than in adults in Belgium, Germany, Romania and the UK. Abou-Elwafa Abdallah et al. (2016) [47] estimated dermal absorption in the UK for TCIPP, TDCIPP and TCEP for adults at 3.8, 0.2 and 0.1 ng/kg bw/d and for toddlers at 32.9, 1.6 and 1.5 ng/kg bw/d, respectively. Dermal intakes were thus higher than via dust ingestion for these three OPFRs for UK adults. The contrary was true for UK children, and also for many OPFRs in car dust in Greece [28], notably for TBOEP and TPHP, which are not volatile making the ingestion of dust the main exposure route. Data suggest that inhalation (including both gaseous and particulate phases) exposure may also be an important pathway [48] especially for more volatile compounds such as TCEP or TCIPP [37]. In Norway, the adult median inhalation exposure to OPFRs was 9.3 ng/kg bw/d, which is similar to dust ingestion exposure (8.9 ng/kg bw/d) [37].

Overall, major indoor pathways seem to differ from one OPFR to another. In European populations, dust ingestion was the major exposure pathway for TBOEP and TPHP, while inhalation was the major exposure route for TCIPP and TCEP. Unlike EHDPP, dietary exposure is negligible for TBOEP, TPHP, TCIPP and TCEP [22]. Dermal absorption is a minor pathway for EHDPP, TBOEP, TCIPP, TCEP and TPHP [22]. No European data were found concerning a major pathway for TDCIPP. However, these observations are issued from few studies with diverse protocols, OPFRs of interest and microenvironments; a comprehensive and systematic study on exposure routes of main OPFRs would be of great interest.

3.2.2. Human Biological Measurements of Exposure

A total of 12 studies that reported concentrations of OPFRs or their metabolites (presented in Table S1 with their parent compounds) in more than ten human samples were identified and reviewed [15,21,35,49–57]. Metabolites were measured in urine, whereas OPFR parents' compounds were measured in hair and milk. OPFRs and metabolites analyzed in matrices were not exactly the same between articles. These studies were conducted in Germany, Belgium, Norway, Sweden and Spain. The data are summarized in Figure 3 (only detected chemicals are displayed) and detailed in supplemental information (Table S4).

A total of 15 metabolites were measured in urinary samples (Figure 3 for detected compounds): Diethyl phosphate (DEP, metabolite of TEP), Bis(2-butoxyethyl) phosphate (BBOEP), Bis(2-butoxyethyl)-(2-hydroxyethyl) phosphate (BBOEHEP) and Di-(2-butoxyethyl) phosphate (DBOEP) (metabolites of TBOEP), Diphenyl phosphate (DPHP, metabolite of TPHP), Diethylhexyl phosphate (DEHP, metabolite of TEHP), Bis-(2-chlorethyl)-phosphate (BCEP) and Di-(2-chloroethyl) phosphate (DCEP) (metabolites of TCEP), Di-n-butyl phosphate (DnBP, metabolite of TNBP), BDCIPP (metabolite of TDCIPP), Bis(1,3-dichloro-2-propyl) phosphate (BCIPP) and Di-(2-chloroisopropyl) phosphate (DCIPP, metabolite of TCIPP), Di-m-cresyl phosphate (DmCP, metabolite of TmCP), Di-o-cresyl phosphate (DoCP, metabolite of ToCP) and Di-p-cresyl phosphate (DpCP, metabolite of TpCP). Samples of urine were collected in Norway, Germany and Belgium from children aged from 20 months to 12 years and adults. Median concentrations ranged from 0.12 ng/L for BDCIPP to 3.2 ng/L for DEP [51,54].

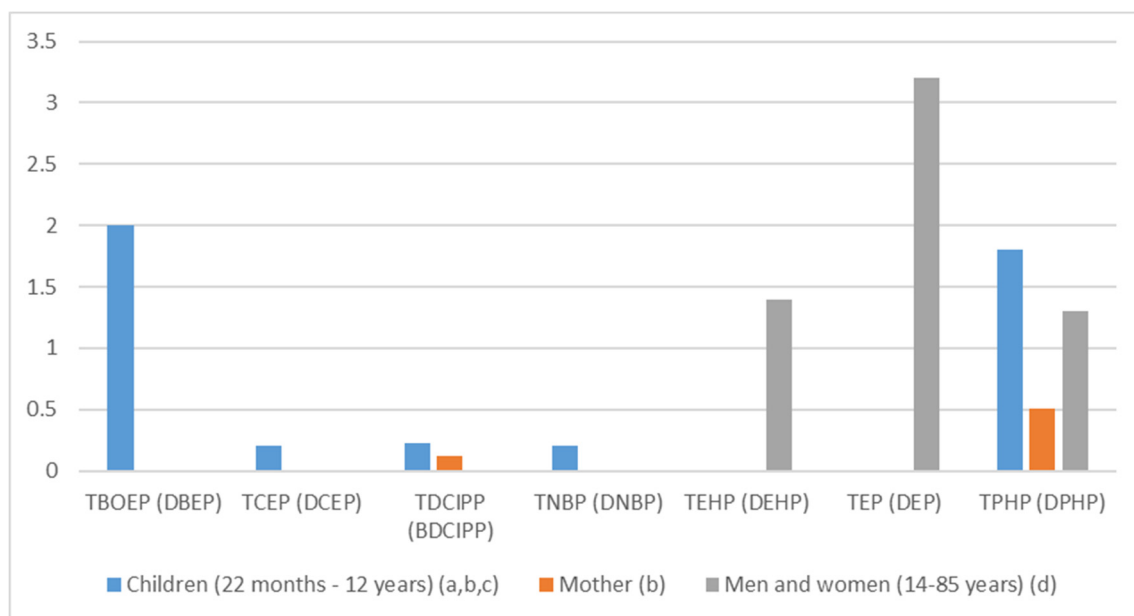


Figure 3. OPFRs (metabolite) highest median urinary concentrations (ng/L) in Europe, 2000–2018 (ng/mL); (a) Fromme et al., 2014 [21]; (b) Cequier et al., 2015 [27]; (c) Larsson et al., 2014 [53]; (d) Reemtsma et al., 2011 [54].

Compounds having median concentrations of metabolites above 1 ng/mL, were TEP > TBOEP > TPHP > TEHP [21,51,54]. In populations including mothers and children (general population, see Figure 3), the metabolite with the highest median concentration was DEP with a median of 3.2 ng/L, followed by DEHP (median = 1.4 ng/L) and DPHP (median = 1.3 ng/L) [54].

In children, the two metabolites with the highest concentration were DBOEP (median = 2 ng/L) [21] and DPHP (median = 1.8 ng/L) [53].

DBOEP, DBP, DPHP and BDCIPP urinary concentrations were measured in samples from both mothers and children [21,50,51,53,57]. DBOEP and DPHP median concentrations were higher in children, whereas DnBP and BDCIPP median concentrations were similar in mothers and children.

The only study to report on OPFR concentrations in hair was conducted in 2012, in Norwegian children aged from 6 to 12 years and their mothers. Seven OPFRs were found: TBOEP, TCEP, TPHP, TDCIPP, EHDPP, TNBP and TMPP (Figure 4). The median concentration ranged from 8 ng/g for TMPP to 318 ng/g for TBOEP [52]. The TBOEP median concentration in children was around five times higher than in mothers, while for other OPFRs the median concentrations were similar. Two studies investigated OPFR concentrations in breastmilk in Sweden and Spain [49,56]. Fifteen OPFRs were measured, ten were detected and their median concentrations ranked as follows: TCIPP > TMP > TBOEP > TNBP > TPHP > EHDPP > TCEP > TDCIPP > TEP > TMPP (Figure 5). TCIPP was predominant, with a median concentration of 45 ng/g of lipid weight. Other OPFR median concentrations ranged from 0.8 to 19 ng/g of lipid weight.

To conclude, OPFRs (or their metabolites) concentrations differ between matrices, likely reflecting different metabolisms. In urine, the OPFR with the highest concentration was DEP (a TEP metabolite), so an estimation of its intake and exposure pathways would be of interest. It is important to stress that DEP is also a degradation product of organophosphorus insecticides such as chlorpyrifos [54]. In children's hair, the most concentrated OPFR was TBOEP, whose intake was high, especially via dust ingestion. The highest concentration in TCEP was noticed in mothers' hair, while the highest concentration of TCIPP was in breastmilk. These OPFRs had a high human intake estimation, mainly via inhalation and dust ingestion [22]. Despite the high TDCIPP human intake via dust ingestion and dermal absorption, concentrations of this OPFR (or its metabolite) in urine, hair and breastmilk appeared very low compared to other OPFRs, which deserves confirmation from other studies.

Considering their widespread environmental occurrence, the biomonitoring of OPFR is likely to develop in the coming years. A great expectation is a comprehensive strategy on the search for metabolites or parent compounds in human matrices, before representative surveys could occur on large populations.

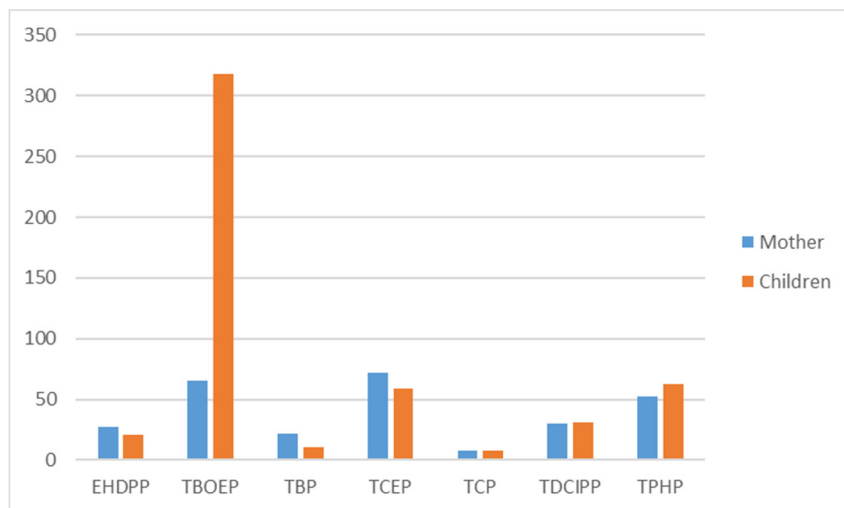


Figure 4. Median OPFR concentrations found in hair in Europe, 2000–2018 [51] (ng/g).

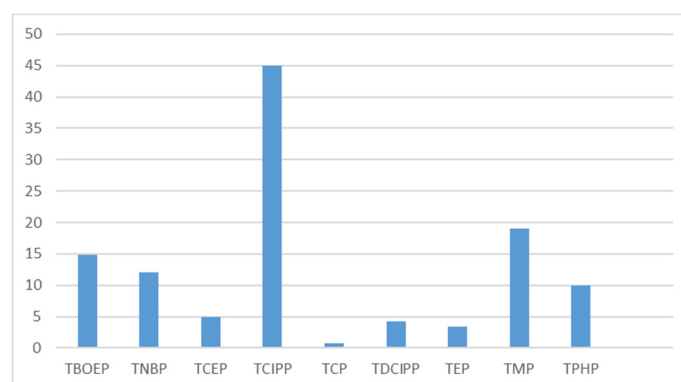


Figure 5. Maximal median OPFR concentrations found in breastmilk in Europe, 2000–2019 (ng/g of lipid weight) [49,56].

This broad review allows us to put indoor concentrations and human exposure in Europe into perspective. TCIPP, TDCIPP and TBOEP had the highest median concentrations in dust samples, and logically the highest estimation for dust ingestion intake. Specifically, TBOEP was measured at high concentrations in daycare centers, but only in Germany, and in children’s hair. TCIPP was measured as having a median concentration ten times higher than TBOEP and TDCIPP in maternal milk, consistent with high dust ingestion TCIPP intake.

3.3. Epidemiological Associations

Since 2000, 19 epidemiological studies have been assessed, mostly in the USA, on the associations between exposure to OPFRs and health effects in humans, and they are presented in Table 1 [40,58–74]. The health outcomes studied were reproductive, thyroid, neurodevelopmental, respiratory, immunotoxic and dermal. Exposure to OPFRs was assessed using house dust, passive wristband, and urine or blood samples. In these studies, metabolites are specific to the OPFR parent compound, with the exception of the TPHP metabolite, because DPHP is also a metabolite of EHDPP and resorcinol bis(diphenyl phosphate) [58,59].

Table 1. Epidemiological evidence on organophosphorus flame retardants, 2000–2019.

Author	Date	Country	Population	Exposure Assessment	Compounds of Interest	Health Outcome	Covariates	Human Health Findings
Doherty et al. [58]	2019	USA	149 children of 36 months	Urine sample collected from mothers between 24- and 29-week gestation	DPHP, BDCIPP, IP-PPP, BCIPHIPP	Children’s cognitive function (Composite, Fine Motor, Visual Reception, Receptive Language, Expressive Language) was assessed using the Mullen Scales of Early Learning (MSEL) at age between 2 and 3 years	Maternal age, education, income, race/ethnicity, BMI, and child’s sex	Concentrations of IP-PPP (ng/mL) were associated with MSEL Cognitive Composite Score ($\beta = -2.61$; 95% CI: $-5.69, 0.46$), Fine Motor Scale ($\beta = -3.08$; 95% CI: $-5.26, -0.91$) and the Expressive Language Scale ($\beta = -1.21$; 95% CI: $-2.91, 0.49$)
			227 children of 36 months	Urine sample collected from mothers between 24- and 29-week gestation	DPHP, BDCIPP, IP-PPP, and BCIPHIPP	Children’s language (Vocabulary, Grammatical Complexity) was assessed using the MacArthur-Bates Communicative Development Inventories (MB-CDI) at age between 2 and 3 years	Maternal age, education, income, race/ethnicity, BMI, and child’s sex	Prenatal IP-PPP concentrations were inversely associated with age-standardized scores on the MB-CDI Vocabulary assessment ($\beta = -1.19$; 95% CI: $-2.53, 0.16$)
Ait Bamai et al. [59]	2018	Japan	296 children	House dust samples collected at age 7 of children	TMP, TEP, TPP, TBP, TCIP TCEP, TEHP, TBEP, TDCPP, TPhP, TCP	Eczema and wheeze were assessed in children aged 7 years using the International Study of Asthma and Allergies in Childhood questionnaire	Sex, household income, maternal smoking, and parental history of atopy.	Among children without any flaggrin mutations, TDCIPP was associated with wheeze (OR: 1.22, 95% CI: 1.00–1.48)
Araki et al. [60]	2018	Japan	128 elementary school-aged children	Multisurface dust	TMP, TEP, TPP, TNBP, TCIPP, TCEP, TEHP, TBEP, TDCPP, TPHP, TMPP	International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire	Sex, grade, annual income, and dampness index	Association between TDCIPP in house dust and eczema (OR:3.75; 95% CI: 1.39, 10.2)
			113 to 128 elementary school-aged children	Urine samples collected from children	5-HO-EHDPHP, EHPHP, BBOEP, 3-HO-TBEP, BBOEHEP, BCIPP, BCIPHIPP, DPHP, 4-HO-DPHP, 3-HO-TPHP, 4-HO-TPHP, BDCIPP, DNBP, uTCEP	International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire	Sex, grade, annual income, dampness index, and creatinine	Association between Σ uTCIPP and rhinoconjunctivitis (4th quartile vs. 1st quartile) (OR= 5.01; 95% CI: 1.53, 6.5; $p = 0.008$), TBEP-OH (>LOD vs. <LOD) and eczema (OR= 2.86; 95% CI: 1.04, 7.85; $p = 0.041$), BDCIPP (3rd tertile vs. 1st tertile) and at least one of the symptoms (wheeze, rhino-conjunctivitis, eczema) (OR= 3.91; 95% CI: 1.24, 12.3; $p = 0.019$)
Carignan et al. [61]	2018	USA	201 couples from the Environment and Reproductive Health (EARTH)	One or two spot urine samples per in vitro fertilization cycle	BCIP, BDCIPP, DPHP, IP-PPP, tb-PPP	Proportion of fertilized oocytes, number of best quality embryos, proportion of cycles resulting in implantation, clinical pregnancy and live birth	Year of IVF treatment cycle, primary infertility diagnosis, and maternal urinary PFR metabolites as well as paternal and maternal age, body mass index, and race/ethnicity.	Paternal urinary concentrations of BDCIPP were associated with fertilization (95% CI: 0.01, 0.12; p -trend = 0.06)
		USA	211 women from the Environment and Reproductive Health (EARTH)	One or two urine samples per IVF cycle	BCIP, BDCIPP, DPHP, IP-PPP, tb-PPP	Proportion of fertilized oocytes, number of best quality embryos, proportion of cycles resulting in implantation, clinical pregnancy and live birth	Maternal age, body mass index, race/ethnicity, year of IVF treatment cycle, and primary Society for Assisted Reproductive Technology (SART) infertility diagnosis at study entry	Association between the levels of two individual metabolites (DPHP and tb-PPP) and of total metabolites , and reduced probability of successful fertilization, implantation, clinical pregnancy, and live birth
Deziel et al. [62]	2018	USA	200 women (100 papillary thyroid cancer cases and 100 controls)	Single spot urine samples	BCIPP, BCIPHIPP, BDCIPP IP-PPP, DPHP and tb-PPP		Age, BMI, education level, family history of thyroid cancer, previous benign thyroid disease, and alcohol consumption	No association between BCIPHIPP , BCIPP , DPHP , BDCIPP , IP-PPP , tb-PPP and papillary thyroid cancer (PTC)

Table 1. Cont.

Author	Date	Country	Population	Exposure Assessment	Compounds of Interest	Health Outcome	Covariates	Human Health Findings
Hoffman et al. [63]	2018	USA	248 pairs women–child	Urine samples collected between 24–30 weeks gestation	BDCIPP, DPHP, IP-PPP, BCIPHIPP, BCIPP, tb-PPP	Gestational age in days (combination of last menstrual period and earliest-ultrasounds data) and birthweight Preterm birth (defined as <37 weeks gestation)	Maternal age, race, education, parity, prepregnancy BMI and season of urine sample collection Maternal age, race, education, parity, prepregnancy BMI and season of urine sample collection	Among female infants, IP-PPP was associated with birth ($\beta = -1.00$ week; 95% CI: $-1.85, -0.15$ weeks; $p = 0.02$). Among male infants, DPHP was associated with gestational duration ($\beta = 0.75$ weeks; 95% CI: 0.01, 1.50 weeks; $p = 0.05$) Among females infants, preterm birth was associated with IP-PPP (OR: 4.58; 95% CI: 1.23, 17.06) and BDCIPP (OR: 3.99; CI: 1.08, 14.78). Among male infants maternal urinary IP-PPP concentrations were associated with preterm birth (OR: 0.21; 95% CI: 0.06, 0.68).
Castorina et al. [64]	2017	USA	248 to 249 pairs women–child	Urine samples collected during the 2nd prenatal study visit Urine samples collected during the 2nd prenatal study visit	BDCIPP, DPHP, IP-PPP, tb-PPP BDCIPP, DPHP, IP-PPP, tb-PPP	Children’s cognitive abilities was assessed by a single bilingual psychometrician at age 7 using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Full-Scale IQ, Working memory, Perceptual reasoning, Verbal comprehension, Processing speed) Children’s behavior was assessed by maternal and teacher report at age 7 using the Behavior Assessment System for Children 2 (BASC-2) (ADHD Index, Inattention DSM-IV, Hyperactive/Impulsive DSM-IV, total subscale DSM-IV) and the Conners’ ADHD/DSM-IV Scales (CADS) (Hyperactivity scale, Attention problems scale)	Maternal education, PPVT scores, CES-D scores, country of birth and prenatal urinary DAP metabolite levels, HOME z-score, language of WISC testing, child sex and age at assessment, and household poverty Sex, age at assessment, maternal country of birth, HOME score at 7-years, prenatal DAPs, and maternal depression and education	Association between DPHP and Full-Scale IQ ($\beta: -2.9$; 95% CI: $-6.3, 0.5$), DPHP and Working memory (WISC-IV scale) ($\beta: -3.9$; 95% CI: $-7.3, -0.5$), SPFR metabolites and Working memory (WISC-IV scale) ($\beta: -4.6$, 95% CI: $-8.9, -0.3$). Association between IP-PPP and Hyperactivity scale (BASC-2—Maternal Report (T-score) ($\beta: 2.4$; 95% CI: 0.1, 4.7), BDCIPP and Attention problems scale (BASC-2—Teacher Report (T-score) ($\beta: 1.1$; 95% CI: $-0.1, 2.3$; $p < 0.1$))
Hoffman et al. [65]	2017	USA	70 cases and 70 controls	Dust samples from homes	TCEP, TCIPP, TDCPP and TPHP	Diagnostic of papillary thyroid cancer (PTC)	Indicator of tumor aggressiveness for FR exposure above the median	Higher levels of TCEP associated with increased odds of PTC (OR: 2.42; 95% CI: (1.10, 5.33))
Lipscomb et al. [66]	2017	USA	72 children aged 3–5 years	Passive wristband samplers worn continuously for 7 days	TPP, TCIPP, TCEP, TDCPP	Children’s social behaviors were assessed using the Social Skills Improvement System-Rating Scales (SSIS-RS) by their teacher in the preschools they were attending (seven subscales representing positive behaviors: Communication, Cooperation, Assertion, Responsibility, Empathy, Engagement, and Self-Control; four subscales representing behavior problem domains: Externalizing, Bullying, Hyperactivity/Inattention, and Internalizing)	Gender, age, family context, and child’s exposure to adverse experiences	In OPFR levels were associated with responsibility ($\beta = -0.25$, $p < 0.001$) and externalizing problems ($\beta = 0.31$, $p < 0.05$)

Table 1. Cont.

Author	Date	Country	Population	Exposure Assessment	Compounds of Interest	Health Outcome	Covariates	Human Health Findings
Preston et al. [67]	2017	USA	51 adults	133 urine samples collected at months 1,6 and 12	DPHP	Free thyroxine (fT4), total thyroxine (TT4), total triiodothyronine (TT3), and thyroid stimulating hormone (TSH) in serum samples	Sampling round, time of sample collection, specific gravity-corrected iodine and BDE-47 and sex	DPHP was associated with a 0.43 µg/dL (95% CI: 0.47, 1.36) increase in mean TT4 levels
			25 women	61 urine samples collected at months 1,6 and 12	DPHP	Free thyroxine (fT4), total thyroxine (TT4), total triiodothyronine (TT3), and thyroid stimulating hormone (TSH) in serum samples	Sampling round, time of sample collection, specific gravity-corrected iodine and BDE-47	DPHP was associated with a 0.91 µg/dL (95% CI: 0.47, 1.36) increase in mean TT4 levels
			26 men	61 urine samples collected at months 1,6 and 12	DPHP	Free thyroxine (fT4), total triiodothyronine (TT3), and thyroid stimulating hormone (TSH) in serum samples	Sampling round, time of sample collection, specific gravity-corrected iodine and BDE-47	No significant association between DPHP and TT4, fT4, TT3, TSH
Soubry et al. [68]	2017	USA	67 men	Urinates samples	BCIPP, BDCIPP, DPHP, IP-PPP, tb-PPP	DNA extracted from sperm samples	Age, obesity-status and multiple testing, exposure to monoisopropylphenyl diphenyl phosphate	Association between BDCIPP, DPHP, IP-PPP and hyper- or hypomethylation of different genes specific to the metabolites
Canbaz et al. [69]	2016	Sweden	110 children who developed asthma at 4 or at 8 years, matched with 110 controls from a large perspective study	Dust collected from the mother's mattress two months after childbirth	TCEP, TCIPP, TDCPP, TBEP, TPhP, EHDPP, mmp-TMPP	Asthma at 4 or 8 years was defined based on at least two of the following three criteria: (i) >1 episode of wheeze in the last 12 months; (ii) a doctor's diagnosis of asthma; (iii) asthma medicine prescribed occasionally or regularly over the last 12 months		No association between PEFs concentrations and development of childhood asthma
Zhao et al. [70]	2016	China	154 men and 101 women	One blood sample	TCIPP, TBEP, TPHP, TEP, TNBP, EHDPP	Blood samples	Negative association between EHDPP, TPHP, and TNBP levels and sphingosine 1-phosphate concentration	Association between levels of the six PEFs and increased sphingomyelin concentration ($p < 0.001$ for all OPFRs). The S1P level in the highest quartile of EHDPP was 36% lower (95% CI: -39% , -33% ; $p < 0.001$) than that in the lowest quartile , 16% lower (95% CI: -19% , -14% ; $p < 0.001$) than that in the highest TPHP quartile , and 36% lower (95% CI: -38% , -33% ; $p < 0.001$) than that in the highest TNBP quartile
Araki et al. [71]	2014	Japan	516 inhabitants (adults and children) in 156 different homes	Floor dust	TMP, TEP, TPE, TNBP, TCIPP, TCEP, TEHP, TBEP, TDCPP, TPHP, TMPP	All inhabitants of each home were asked to complete a self-administered questionnaire participants who reported having received medical treatment for bronchial asthma, atopic dermatitis, allergic rhinitis, and/or allergic conjunctivitis at any time during the preceding 2 years were classified as positive	Gender, age, tobacco smoke, ETS exposure, recent renovations, wall-to-wall carpeting, dampness index, hair/fur-bearing pets in the dwelling, mechanical ventilation equipment usage, and total fungi	Association between TNBP in multi-surface dust and asthma (OR: 5.34; 95% CI: 1.45, 19.7), TNBP in multi-surface dust and allergic rhinitis (OR: 2.55; 95% CI: 1.29, 45.01)

Table 1. Cont.

Author	Date	Country	Population	Exposure Assessment	Compounds of Interest	Health Outcome	Covariates	Human Health Findings
Meeker et al. [72]	2013	USA	33 men	Urine samples	BDCIPP, DPHP	Blood and semen samples	Age, BMI, and time of sample collection, abstinence period	Association between BDCIPP levels and decreases in sperm quality parameters, and concentrations of total T3 (% change: 6.6; 95% CI: 1.6,12.8, $p = 0.02$) and TSH in serum (% change: 40.3; 95% IC: 11.4, 77.1, $p = 0.006$). DPHP was associated with a 57% (95% CI: -77.8, -18.8, $p = 0.01$) decrease in sperm concentration and a 20% (95% CI: -41.1, 0.5) decrease in sperm motility
Hutter et al. [32]	2013	Austria	436 children	Air	TCEP, TDCPP	The cognitive evaluation was accomplished by a neurodevelopment test	Social status, gender and region (urban/rural)	Significant correlations of TCEP in PM10 and PM2.5 and school dust samples with cognitive performance . Cognitive performance decreased with increasing concentrations of TCEP
Bergh et al. [40]	2011	Sweden	Adults (men and women)	Air	TEP, TiPrP, TPPrP, TiBP, TBP, TCEP, TCIPP, TPeP, THP, TDCPP, TPP, DPEHP, TEHP, TToP, d27-TBP cis			No association between OPFRs levels and reported Sick Building Syndrome symptoms
Kanazawa et al. [73]	2010	Japan	134 adults (70 women and 64 men)	Floor dust	TBP, TBEP, TDCPP		Age (ordinal variable in increments of 10 years), gender, history of allergy, time spent at home (h/day; ≤ 12 , > 12), and condensation and moldy odor	Association between TBP and mucosal symptoms of Sick Building Syndrome (OR: 15, 95% CI: 2.7–80), TBOEP (OR: 0.3, 95% CI: 0.1–0.7), TDCIPP (OR: 2.2, 95% CI: 1.0–4.6)
Meeker et al. [74]	2009	USA	38 men 50 men	House dust	TDCPP, TPP	Serum and semen samples: hormones (Free T4, Total T3, TSH, FSH, LH, Inhibin B, Testosterone, SHBG, FAL, estradiol, Prolactin, Sperm concentration, sperm mobility, sperm morphology)	Age, BMI Age, BMI and abstinence period	Association between TDCIPP and Free T4 (β : -2.8; 95% CI: -4.6, -1.0; p : 0.004), TDCPP and prolactin (β :17.3; 95% CI: 4.1–32.2; p : 0.008), TPP and prolactin (β : 9.7; 95% CI: 2.3,18.9; p : 0.02) Association between TPP and sperm concentration (β : -18.8; 95% CI: -30.1, -4.5; p : 0.01)

Bold: Key elements of the table.

Reproductive functions: Three OPFR, TDCIPP, TPHP and Isopropylated triarylphosphate isomers (ITPs) (or their metabolites) were tested for possible impacts on the reproductive system. Of 201 couples undergoing in vitro fertilization, the urinary TDCIPP metabolite concentrations among the men (though not the women) were associated with a reduced probability of successful oocyte fertilization [61]. In another study, urinary concentrations of the TDCIPP metabolite were cross-sectionally associated with a decrease in both sperm quality parameters (sperm motility, sperm morphology, straight lie velocity and curvilinear velocity) and the thyroid-stimulating hormone (TSH) levels that prompt the thyroid gland to produce hormones [72]. An inverse association was observed between TDCIPP house dust concentrations and occupants' prolactin hormonal levels in serum [74]. Among female infants, the maternal TDCIPP and ITP metabolite concentrations measured in urine samples collected during the late-second or early-third trimester were associated with an increased risk of preterm birth [63]. Conversely, among male infants, the maternal ITP metabolite concentrations measured in urine samples collected during the late-second or early-third trimester were associated with a decreased risk of preterm birth [63]. The TPHP metabolite concentrations measured in urine samples collected during in vitro fecundation from women were inversely associated with the probability of successful fertilization (presence of a fertilized oocyte with two pronuclei 17–20 h after insemination), implantation (defined as a serum β -hCG level > 6 mIU = mL, approximately 17 d (range = 15–20 d) after egg retrieval), clinical pregnancy (the presence of an intrauterine pregnancy confirmed by ultrasound at approximately 6-week gestation) and live birth (defined as the birth of a neonate on or after 24-week gestation) [61]. Another study observed an association between house dust TPHP concentration and decrease in sperm concentration among 50 men from couples that were infertile due to a male factor, a female factor, or a combination of both [74]. The same study observed an association between house dust TPHP concentration and an increase in serum prolactin hormone levels in a population of 38 men [74]. Among male infants, urinary TPHP metabolite concentrations were associated with a modest increase in gestational duration. Baby boys having the highest levels of prenatal TPHP exposure were born approximately 5 days later than those with the lowest levels of exposure [63].

Thyroid systems: Three OPFRs, TDCIPP, TPHP and TCEP (or their metabolites), were tested for possible impacts on the thyroid system. TDCIPP metabolite urinary concentrations were associated with a decrease in concentrations of total triiodothyronine (T3 hormone that helps regulate various physiological processes including growth, metabolism, body temperature and cardiac rhythm), measured cross-sectionally in serum [72]. A positive association was found between TPHP metabolite urinary concentrations and mean total thyroxine levels measured cross-sectionally in serum (T4 hormone, mainly secreted by the thyroid gland, and essential for proper metabolic functioning) among women, but not in men [67]. The TDCIPP urinary metabolite concentrations measured in women from a case-control study (100 cases and 100 controls) were not associated with an increased risk of papillary thyroid cancer [62]. The TCEP concentrations measured in house dust samples were associated with an increased risk of papillary thyroid cancer in women from a case-control study (70 cases and 70 controls) [65].

Neurodevelopmental outcomes: TDCIPP, TPHP and ITP have been studied to assess their effect on neurodevelopment. Prenatal urinary TDCIPP metabolite concentrations were positively associated with attention problems (measured using the Behavior Assessment System for Children-2 scale—Teacher Report) among 7-year-olds [64]. This study found no association between prenatal urinary TDCIPP metabolite concentrations and the hyperactivity scale among children aged 7 [64]. Prenatal urinary TPHP metabolite concentrations were associated with a decrease in intellectual quotient assessed by the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV), among children at age 7, and particularly for the working memory domain [64]. Prenatal urinary ITP metabolite concentration was inversely associated with age-standardized scores on the MacArthur-Bates Communicative Development Inventories vocabulary assessment, Mullen Scales of Early Learning cognitive composite score, fine motor scale and expressive language scale at age 36 months [58]. Furthermore, prenatal concentrations of this metabolite were positively associated with higher scores

on the hyperactivity scale at age 7 [64] in the California area, where Firemaster[®] 550 (containing ITPs, Great Lakes Solutions, Chemtura Corporation, Philadelphia, PA, USA.) was used.

Respiratory outcomes and immunotoxicity: Three OPFRs, TDCIPP, TCIPP and TNBP, or their metabolites, were tested for possible effects on the respiratory system or immunotoxicity. TDCIPP measured in house dust samples was associated with an increased risk of wheezing in children 7 years of age [59], though not with asthma among children aged 4–8 years [69]. A positive association between urinary TCIPP metabolite concentrations and an increased risk of rhino-conjunctivitis was cross-sectionally observed among children aged 6–12 years [60]. TCIPP measured in house dust two months after birth was not associated with the development of asthma at 4 or 8 years in a case-control study (110 cases and 110 controls) [69]. In the cross-sectional study conducted by Araki et al. [71], the authors did not observe any association between an increased risk of allergic rhinitis in adults and children and TCIPP concentration in house dust. On the contrary, they found a positive association between TNBP concentrations in house dust and risk of asthma among children and adults, as well as an increased risk of allergic rhinitis [60].

Dermal effects: Only one study [60] tested for an association between increased risk of eczema and TDCIPP. Eczema was evaluated using the International Study of Asthma and Allergies in Childhood (ISAAC), while exposure assessed using TDCIPP in house dust and TBOEP urinary metabolites and TCIPP (or its metabolite BCIPP) was cross-sectionally associated with eczema in school-aged children [60].

Other outcomes: Blood concentrations of six OPFRs (TCIPP, TBOEP, TPHP, TEP, TNBP and EHDPP) independently increased sphingomyelin concentrations (which participate in cardiovascular function) in blood among adults [70]. Otherwise, TBOEP indoor concentrations in air were associated with an increased risk of sick building syndrome in Japan [73].

In conclusion, both TDCIPP and TPHP were consistently associated with multiple health outcomes, mainly reproductive. High TCIPP concentrations were possibly associated with adverse respiratory outcomes when exposure was assessed via measurement in human samples, but not when assessed by measurement in indoor environments. Two epidemiological studies associated the ITP urinary metabolite concentrations during pregnancy with various neurodevelopmental outcomes among children in North America. Globally, most epidemiologic studies have addressed relatively modest population sample sizes and thus were limited in statistical power. Considering OPFRs in large epidemiological studies would be useful, especially for compounds widely measured in human environments and matrices such as TBOEP and TNBP.

4. Conclusions

Due to an increase in their use, a significant OPFR presence was observed in both indoor environments and human biological matrices in Europe. In this review, we chose to have a broad spectrum from contamination to health effects in humans, complementary to more detailed reviews that exist on specific aspects. We tabulated our findings in Table 2, and summarized them in Figure 6, with the objective to contribute to identifying the prevention and research areas that should be priorities. The most concentrated OPFRs in dust were TBOEP, TCIPP and TDCIPP, and in the air, TCIPP and TNBP. These OPFRs deserve to be studied in more microenvironments in larger and representative surveys. Of these OPFRs, both TBOEP and TCIPP were also found to have the highest concentrations in human matrices, especially among children. TDCIPP and TNBP were also observed in human matrices, however these were among the lowest concentrations. These findings rely on few studies and need to be confirmed on larger representative samples. TDCIPP is one of the most investigated OPFRs in association studies, and has been linked with multiple health outcomes, while TPHP is associated with reproductive outcomes. Considering widespread exposure and epidemiological evidence for these two OPFRs, health risk assessment, including a more systematic assessment of relative importance of different microenvironments and exposure routes, may be useful in informing decision making about preventive actions. While TBOEP and TNBP were frequently found in both indoor environments

and human matrices, especially in children, association studies have mostly investigated respiratory outcomes, so epidemiological studies would be a priority for these compounds. Table 2 also indicates that several OPFRs have occasionally been studied and detected indoors, so both confirmation studies and a search in biological matrices would be of interest. Lastly, there is a lack of European data concerning Isopropylphenyl phenyl phosphate (IP-PPP) concentrations in both indoor environments and human matrices that must be investigated. Moreover, its classification as potentially neurotoxic and reprotoxic for the fetus (Vermont Department of Health) might incite further epidemiological studies with enough statistical power to assess a potential effect on neurodevelopmental outcomes. More generally, neurodevelopmental outcomes appear to have been studied less than other health effects and may deserve specific attention.

Table 2. Summary of OPFRs indoor contamination, population exposure in Europe and epidemiologic evidence.

Compound	Indoor Contamination	Human Exposure	Epidemiological Evidence of Adverse Effect				
			Reproductive	Thyroid	Respiratory/Immune	Neuro-Development	Dermal
BCMP-BCEP							
BDP							
DPHP							
EHDPP							
iDDPHP							
iDPP							
ITP							
PBDPP							
TBOEP							
TBPP							
TCEP							
TCIPP							
TDBPP							
TDCIPP							
TEHP							

Table 2. Cont.

Compound	Indoor Contamination	Human Exposure	Epidemiological Evidence of Adverse Effect				
			Reproductive	Thyroid	Respiratory/Immune	Neuro-Development	Dermal
TEP							
THP							
TIBP							
TIPP							
TiPPP							
TmCP							
TMP							
TMPP							
TNBP							
ToCP							
TpCP							
TPEP							
TPHP							
TPP							
TXP							

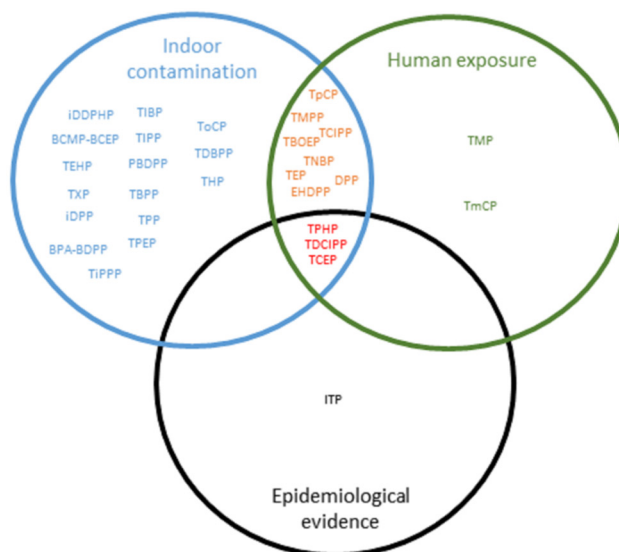


Figure 6. Schematic overview of indoor contamination, human exposure in Europe and epidemiologic evidence of organophosphorus flame retardants. 2000–2019.

Supplementary Materials: The following are available online at <http://www.mdpi.com/1660-4601/17/18/6713/s1>, Table S1. OPFRs abbreviation; Table S2. Concentrations of OPFRs in indoor dust ($\mu\text{g/g}$), Europe, 2000–2018; Table S3. Concentrations of OPFRs in indoor air (ng/m^3), Europe, 2000–2018; Table S4. Human exposure to OPFRs, Europe, 2000–2019.

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References

1. Kemmlein, S.; Hahn, O.; Jann, O. Emissions of organophosphate and brominated flame retardants from selected consumer products and building materials. *Atmos. Environ.* **2003**, *37*, 5485–5493. [CrossRef]
2. European Flame Retardant Association. Frequently Asked Questions on Flame Retardants. Available online: <https://docplayer.net/11069706-Flame-retardants-frequently-asked-questions-the-european-flame-retardants-association.html> (accessed on 10 July 2020).
3. Building Evidence for Health. Available online: https://buildingevidence.forhealth.org/wp-content/uploads/sites/2/2017/05/ForHealth.org_FlameRetardants.pdf (accessed on 10 July 2020).
4. Blum, A.; Behl, M.; Birnbaum, L.S.; Diamond, M.L.; Phillips, A.; Singla, V.; Sipes, N.S.; Stapleton, H.M.; Venier, M. Organophosphate Ester Flame Retardants: Are They a Regrettable Substitution for Polybrominated Diphenyl Ethers? *Environ. Sci. Technol. Lett.* **2019**, *6*, 638–649. [CrossRef] [PubMed]
5. European Commission. Commission Regulation (EU) 2017/227 of 9 February 2017 Amending Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council Concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as Regards Bis(Pentabromophenyl)Ether. Available online: <http://data.europa.eu/eli/reg/2017/227/oj> (accessed on 12 September 2020).
6. European Union Commission Directive. Directive 2014/79/EU. Available online: <https://eur-lex.europa.eu/legal-content/FR/TXT/HTML/?uri=CELEX:32014L0079> (accessed on 12 September 2020).

7. European Union Commission Directive. Directive 2003/11/EC of the European Parliament and of the Council of 6 February 2003 Amending for the 24th time Council Directive 76/769/EEC Relating to Restrictions on the Marketing and Use of Certain Dangerous Substances and Preparations (Pentabromodiphenyl Ether, Octabromodiphenyl Ether). Available online: <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:042:0045:0046:EN:PDF> (accessed on 3 June 2019).
8. Stockholm Convention, UNEP/POPS/POPRC.4/18 Listing of Tetrabromodiphenyl Ether and Pentabromodiphenyl Ether. Available online: <https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiOuZmNqurrAhVFzKQKHZseBscQFjAAegQIBRAB&url=http%3A%2F%2Fchm.pops.int%2FPortals%2F0%2Fdownload.aspx%3Fd%3DUNEP-POPS-COP.4-SC-4-18.English.pdf&usq=AOvVaw0DuNRdjsPaLgaK481RHSIn> (accessed on 14 September 2020).
9. Covaci, A.; Harrad, S.; Abdallah, M.A.-E.; Ali, N.; Law, R.J.; Herzke, D.; de Wit, C.A. Novel brominated flame retardants: A review of their analysis, environmental fate and behaviour. *Environ. Int.* **2011**, *37*, 532–556. [[CrossRef](#)] [[PubMed](#)]
10. Van der Veen, I.; de Boer, J. Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis. *Chemosphere* **2012**, *88*, 1119–1153. [[CrossRef](#)] [[PubMed](#)]
11. Pinfa. Non-Halogenated Phosphorus, Inorganic and Nitrogen Flame Retardants 2017. Available online: https://www.pinfa.eu/wp-content/uploads/2018/05/pinfa_BC_edit-2017-web.pdf (accessed on 10 July 2020).
12. Andresen, J.A.; Grundmann, A.; Bester, K. Organophosphorus flame retardants and plasticisers in surface waters. *Sci. Total Environ.* **2004**, *332*, 155–166. [[CrossRef](#)]
13. Mendelsohn, E.; Hagopian, A.; Hoffman, K.; Butt, C.M.; Lorenzo, A.; Congleton, J.; Webster, T.F.; Stapleton, H.M. Nail polish as a source of exposure to triphenyl phosphate. *Environ. Int.* **2016**, *86*, 45–51. [[CrossRef](#)]
14. Marklund, A.; Andersson, B.; Haglund, P. Traffic as a Source of Organophosphorus Flame Retardants and Plasticizers in Snow. *Environ. Sci. Technol.* **2005**, *39*, 3555–3562. [[CrossRef](#)]
15. Schindler, B.K.; Weiss, T.; Schütze, A.; Koslitz, S.; Broding, H.C.; Bünger, J.; Brüning, T. Occupational exposure of air crews to tricresyl phosphate isomers and organophosphate flame retardants after fume events. *Archiv. Toxicol.* **2013**, *87*, 645–648. [[CrossRef](#)]
16. Kojima, H.; Takeuchi, S.; Itoh, T.; Iida, M.; Kobayashi, S.; Yoshida, T. In vitro endocrine disruption potential of organophosphate flame retardants via human nuclear receptors. *Toxicology* **2013**, *314*, 76–83. [[CrossRef](#)]
17. Behl, M.; Hsieh, J.-H.; Shafer, T.J.; Mundy, W.R.; Rice, J.R.; Boyd, W.A.; Freedman, J.H.; Hunter, E.S.; Jarema, K.A.; Padilla, S.; et al. Use of alternative assays to identify and prioritize organophosphorus flame retardants for potential developmental and neurotoxicity. *Neurotoxicol. Teratol.* **2015**, *52*, 181–193. [[CrossRef](#)]
18. Langer, S.; Fredricsson, M.; Weschler, C.J.; Bekö, G.; Strandberg, B.; Remberger, M.; Toftum, J.; Clausen, G. Organophosphate esters in dust samples collected from Danish homes and daycare centers. *Chemosphere* **2016**, *154*, 559–566. [[CrossRef](#)] [[PubMed](#)]
19. Bergh, C.; Torgrip, R.; Emenius, G.; Östman, C. Organophosphate and phthalate esters in air and settled dust—A multi-location indoor study: Organophosphate and phthalate esters in air and settled dust. *Indoor Air* **2011**, *21*, 67–76. [[CrossRef](#)] [[PubMed](#)]
20. Luongo, G.; Östman, C. Organophosphate and phthalate esters in settled dust from apartment buildings in Stockholm. *Indoor Air* **2016**, *26*, 414–425. [[CrossRef](#)] [[PubMed](#)]
21. Fromme, H.; Lahrz, T.; Kraft, M.; Fembacher, L.; Mach, C.; Dietrich, S.; Burkardt, R.; Völkel, W.; Göen, T. Organophosphate flame retardants and plasticizers in the air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3). *Environ. Int.* **2014**, *71*, 158–163. [[CrossRef](#)] [[PubMed](#)]
22. Xu, F.; Tay, J.-H.; Covaci, A.; Padilla-Sánchez, J.A.; Papadopoulou, E.; Haug, L.S.; Neels, H.; Sellström, U.; de Wit, C.A. Assessment of dietary exposure to organohalogen contaminants, legacy and emerging flame retardants in a Norwegian cohort. *Environ. Int.* **2017**, *102*, 236–243. [[CrossRef](#)]
23. Ballesteros-Gómez, A.; Aragón, Á.; Van den Eede, N.; de Boer, J.; Covaci, A. Impurities of Resorcinol Bis(Diphenyl Phosphate) in Plastics and Dust Collected on Electric/Electronic Material. *Environ. Sci. Technol.* **2016**, *50*, 1934–1940. [[CrossRef](#)]
24. Björnsdotter, M.K.; Romera-García, E.; Borrull, J.; de Boer, J.; Rubio, S.; Ballesteros-Gómez, A. Presence of diphenyl phosphate and aryl-phosphate flame retardants in indoor dust from different microenvironments in Spain and the Netherlands and estimation of human exposure. *Environ. Int.* **2018**, *112*, 59–67. [[CrossRef](#)]

25. Brommer, S.; Harrad, S.; Van den Eede, N.; Covaci, A. Concentrations of organophosphate esters and brominated flame retardants in German indoor dust samples. *J. Environ. Monit.* **2012**, *14*, 2482. [[CrossRef](#)]
26. Brommer, S.; Harrad, S. Sources and human exposure implications of concentrations of organophosphate flame retardants in dust from UK cars, classrooms, living rooms, and offices. *Environ. Int.* **2015**, *83*, 202–207. [[CrossRef](#)]
27. Cequier, E.; Ionas, A.C.; Covaci, A.; Marcé, R.M.; Becher, G.; Thomsen, C. Occurrence of a Broad Range of Legacy and Emerging Flame Retardants in Indoor Environments in Norway. *Environ. Sci. Technol.* **2014**, *48*, 6827–6835. [[CrossRef](#)]
28. Christia, C.; Poma, G.; Besis, A.; Samara, C.; Covaci, A. Legacy and emerging organophosphorus flame retardants in car dust from Greece: Implications for human exposure. *Chemosphere* **2018**, *196*, 231–239. [[CrossRef](#)] [[PubMed](#)]
29. Coelho, S.D.; Sousa, A.C.A.; Isobe, T.; Kim, J.-W.; Kunisue, T.; Nogueira, A.J.A.; Tanabe, S. Brominated, chlorinated and phosphate organic contaminants in house dust from Portugal. *Sci. Total Environ.* **2016**, *569–570*, 442–449. [[CrossRef](#)] [[PubMed](#)]
30. Dirtu, A.C.; Ali, N.; Van den Eede, N.; Neels, H.; Covaci, A. Country specific comparison for profile of chlorinated, brominated and phosphate organic contaminants in indoor dust. Case study for Eastern Romania, 2010. *Environ. Int.* **2012**, *49*, 1–8. [[CrossRef](#)] [[PubMed](#)]
31. Harrad, S.; Brommer, S.; Mueller, J.F. Concentrations of organophosphate flame retardants in dust from cars, homes, and offices: An international comparison. *Emerg. Contam.* **2016**, *2*, 66–72. [[CrossRef](#)]
32. Hutter, H.-P.; Haluza, D.; Piegler, K.; Hohenblum, P.; Fröhlich, M.; Scharf, S.; Uhl, M.; Damberger, B.; Tappler, P.; Kundi, M.; et al. Semivolatile compounds in schools and their influence on cognitive performance of children. *Int. J. Occup. Med. Environ. Health* **2013**, *26*. [[CrossRef](#)] [[PubMed](#)]
33. Kademoglou, K.; Xu, F.; Padilla-Sanchez, J.A.; Haug, L.S.; Covaci, A.; Collins, C.D. Legacy and alternative flame retardants in Norwegian and UK indoor environment: Implications of human exposure via dust ingestion. *Environ. Int.* **2017**, *102*, 48–56. [[CrossRef](#)]
34. Sugeng, E.J.; Leonards, P.E.G.; van de Bor, M. Brominated and organophosphorus flame retardants in body wipes and house dust, and an estimation of house dust hand-loadings in Dutch toddlers. *Environ. Res.* **2017**, *158*, 789–797. [[CrossRef](#)]
35. Van den Eede, N.; Neels, H.; Jorens, P.G.; Covaci, A. Analysis of organophosphate flame retardant diester metabolites in human urine by liquid chromatography electrospray ionisation tandem mass spectrometry. *J. Chromatogr. A* **2013**, *1303*, 48–53. [[CrossRef](#)]
36. Vykoukalová, M.; Venier, M.; Vojta, Š.; Melymuk, L.; Bečanová, J.; Romanak, K.; Prokeš, R.; Okeme, J.O.; Saini, A.; Diamond, M.L.; et al. Organophosphate esters flame retardants in the indoor environment. *Environ. Int.* **2017**, *106*, 97–104. [[CrossRef](#)]
37. Xu, F.; Giovanoulis, G.; van Waes, S.; Padilla-Sanchez, J.A.; Papadopoulou, E.; Magnér, J.; Haug, L.S.; Neels, H.; Covaci, A. Comprehensive Study of Human External Exposure to Organophosphate Flame Retardants via Air, Dust, and Hand Wipes: The Importance of Sampling and Assessment Strategy. *Environ. Sci. Technol.* **2016**, *50*, 7752–7760. [[CrossRef](#)]
38. Zhou, L.; Hiltcher, M.; Püttmann, W. Occurrence and human exposure assessment of organophosphate flame retardants in indoor dust from various microenvironments of the Rhine/Main region, Germany. *Indoor Air* **2017**, *27*, 1113–1127. [[CrossRef](#)]
39. Wei, G.-L.; Li, D.-Q.; Zhuo, M.-N.; Liao, Y.-S.; Xie, Z.-Y.; Guo, T.-L.; Li, J.-J.; Zhang, S.-Y.; Liang, Z.-Q. Organophosphorus flame retardants and plasticizers: Sources, occurrence, toxicity and human exposure. *Environ. Pollut.* **2015**, *196*, 29–46. [[CrossRef](#)]
40. Bergh, C.; Magnus Åberg, K.; Svartengren, M.; Emenius, G.; Östman, C. Organophosphate and phthalate esters in indoor air: A comparison between multi-storey buildings with high and low prevalence of sick building symptoms. *J. Environ. Monit.* **2011**, *13*, 2001. [[CrossRef](#)]
41. Wong, F.; de Wit, C.A.; Newton, S.R. Concentrations and variability of organophosphate esters, halogenated flame retardants, and polybrominated diphenyl ethers in indoor and outdoor air in Stockholm, Sweden. *Environ. Pollut.* **2018**, *240*, 514–522. [[CrossRef](#)]
42. Zhou, L.; Hiltcher, M.; Gruber, D.; Püttmann, W. Organophosphate flame retardants (OPFRs) in indoor and outdoor air in the Rhine/Main area, Germany: Comparison of concentrations and distribution profiles in different microenvironments. *Environ. Sci. Pollut. Res.* **2017**, *24*, 10992–11005. [[CrossRef](#)]

43. Persson, J.; Wang, T.; Hagberg, J. Organophosphate flame retardants and plasticizers in indoor dust, air and window wipes in newly built low-energy preschools. *Sci. Total Environ.* **2018**, *628–629*, 159–168. [[CrossRef](#)]
44. Alves, A.; Kucharska, A.; Erratico, C.; Xu, F.; Den Hond, E.; Koppen, G.; Vanermen, G.; Covaci, A.; Voorspoels, S. Human biomonitoring of emerging pollutants through non-invasive matrices: State of the art and future potential. *Anal. Bioanal. Chem.* **2014**, *406*, 4063–4088. [[CrossRef](#)]
45. De Boer, J.; Ballesteros-Gómez, A.; Leslie, H.A.; Brandsma, S.H.; Leonards, P.E.G. Flame retardants: Dust—And not food—Might be the risk. *Chemosphere* **2016**, *150*, 461–464. [[CrossRef](#)]
46. Van den Eede, N.; Dirtu, A.C.; Neels, H.; Covaci, A. Analytical developments and preliminary assessment of human exposure to organophosphate flame retardants from indoor dust. *Environ. Int.* **2011**, *37*, 454–461. [[CrossRef](#)] [[PubMed](#)]
47. Abou-Elwafa Abdallah, M.; Pawar, G.; Harrad, S. Human dermal absorption of chlorinated organophosphate flame retardants; implications for human exposure. *Toxicol. Appl. Pharmacol.* **2016**, *291*, 28–37. [[CrossRef](#)]
48. Stapleton, H.M.; Klosterhaus, S.; Eagle, S.; Fuh, J.; Meeker, J.D.; Blum, A.; Webster, T.F. Detection of Organophosphate Flame Retardants in Furniture Foam and US House Dust. *Environ. Sci. Technol.* **2009**, *43*, 7490–7495. [[CrossRef](#)]
49. Beser, M.I.; Pardo, O.; Beltrán, J.; Yusà, V. Determination of 21 perfluoroalkyl substances and organophosphorus compounds in breast milk by liquid chromatography coupled to orbitrap high-resolution mass spectrometry. *Anal. Chim. Acta* **2019**, *1049*, 123–132. [[CrossRef](#)] [[PubMed](#)]
50. Cequier, E. A high-throughput method for determination of metabolites of organophosphate flame retardants in urine by ultra performance liquid chromatography–high resolution mass spectrometry. *Anal. Chim. Acta* **2014**, *845*, 98–104. [[CrossRef](#)]
51. Cequier, E.; Sakhi, A.K.; Marcé, R.M.; Becher, G.; Thomsen, C. Human exposure pathways to organophosphate triesters—A biomonitoring study of mother–child pairs. *Environ. Int.* **2015**, *75*, 159–165. [[CrossRef](#)]
52. Kucharska, A.; Cequier, E.; Thomsen, C.; Becher, G.; Covaci, A.; Voorspoels, S. Assessment of human hair as an indicator of exposure to organophosphate flame retardants. Case study on a Norwegian mother–child cohort. *Environ. Int.* **2015**, *83*, 50–57. [[CrossRef](#)]
53. Larsson, K.; de Wit, C.A.; Sellström, U.; Sahlström, L.; Lindh, C.H.; Berglund, M. Brominated Flame Retardants and Organophosphate Esters in Preschool Dust and Children’s Hand Wipes. *Environ. Sci. Technol.* **2018**, *52*, 4878–4888. [[CrossRef](#)]
54. Reemtsma, T.; Lingott, J.; Roegler, S. Determination of 14 monoalkyl phosphates, dialkyl phosphates and dialkyl thiophosphates by LC-MS/MS in human urinary samples. *Sci. Total Environ.* **2011**, *409*, 1990–1993. [[CrossRef](#)]
55. Schindler, B.K.; Förster, K.; Angerer, J. Determination of human urinary organophosphate flame retardant metabolites by solid-phase extraction and gas chromatography–tandem mass spectrometry. *J. Chromatogr. B* **2009**, *877*, 375–381. [[CrossRef](#)]
56. Sundkvist, A.M.; Olofsson, U.; Haglund, P. Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. *J. Environ. Monit.* **2010**, *12*, 943. [[CrossRef](#)]
57. Völkel, W.; Fuchs, V.; Wöckner, M.; Fromme, H. Toxicokinetic of tris(2-butoxyethyl) phosphate (TBOEP) in humans following single oral administration. *Arch. Toxicol.* **2018**, *92*, 651–660. [[CrossRef](#)]
58. Doherty, B.T.; Hoffman, K.; Keil, A.P.; Engel, S.M.; Stapleton, H.M.; Goldman, B.D.; Olshan, A.F.; Daniels, J.L. Prenatal exposure to organophosphate esters and cognitive development in young children in the Pregnancy, Infection, and Nutrition Study. *Environ. Res.* **2019**, *169*, 33–40. [[CrossRef](#)]
59. Ait Bamai, Y.; Araki, A.; Nomura, T.; Kawai, T.; Tsuboi, T.; Kobayashi, S.; Miyashita, C.; Takeda, M.; Shimizu, H.; Kishi, R. Association of filaggrin gene mutations and childhood eczema and wheeze with phthalates and phosphorus flame retardants in house dust: The Hokkaido study on Environment and Children’s Health. *Environ. Int.* **2018**, *121*, 102–110. [[CrossRef](#)]
60. Araki, A.; Bastiaensen, M.; Ait Bamai, Y.; Van den Eede, N.; Kawai, T.; Tsuboi, T.; Ketema, R.M.; Covaci, A.; Kishi, R. Associations between allergic symptoms and phosphate flame retardants in dust and their urinary metabolites among school children. *Environ. Int.* **2018**, *119*, 438–446. [[CrossRef](#)]
61. Carignan, C.C.; Mínguez-Alarcón, L.; Williams, P.L.; Meeker, J.D.; Stapleton, H.M.; Butt, C.M.; Toth, T.L.; Ford, J.B.; Hauser, R. Paternal urinary concentrations of organophosphate flame retardant metabolites, fertility measures, and pregnancy outcomes among couples undergoing in vitro fertilization. *Environ. Int.* **2018**, *111*, 232–238. [[CrossRef](#)]

62. Deziel, N.C.; Yi, H.; Stapleton, H.M.; Huang, H.; Zhao, N.; Zhang, Y. A case-control study of exposure to organophosphate flame retardants and risk of thyroid cancer in women. *BMC Cancer* **2018**, *18*. [[CrossRef](#)]
63. Hoffman, K.; Stapleton, H.M.; Lorenzo, A.; Butt, C.M.; Adair, L.; Herring, A.H.; Daniels, J.L. Prenatal exposure to organophosphates and associations with birthweight and gestational length. *Environ. Int.* **2018**, *116*, 248–254. [[CrossRef](#)]
64. Castorina, R.; Butt, C.; Stapleton, H.M.; Avery, D.; Harley, K.G.; Holland, N.; Eskenazi, B.; Bradman, A. Flame retardants and their metabolites in the homes and urine of pregnant women residing in California (the CHAMACOS cohort). *Chemosphere* **2017**, *179*, 159–166. [[CrossRef](#)]
65. Hoffman, K.; Lorenzo, A.; Butt, C.M.; Hammel, S.C.; Henderson, B.B.; Roman, S.A.; Scheri, R.P.; Stapleton, H.M.; Sosa, J.A. Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. *Environ. Int.* **2017**, *107*, 235–242. [[CrossRef](#)]
66. Lipscomb, S.T.; McClelland, M.M.; MacDonald, M.; Cardenas, A.; Anderson, K.A.; Kile, M.L. Cross-sectional study of social behaviors in preschool children and exposure to flame retardants. *Environ. Health* **2017**, *16*. [[CrossRef](#)]
67. Preston, E.V.; McClean, M.D.; Claus Henn, B.; Stapleton, H.M.; Braverman, L.E.; Pearce, E.N.; Makey, C.M.; Webster, T.F. Associations between urinary diphenyl phosphate and thyroid function. *Environ. Int.* **2017**, *101*, 158–164. [[CrossRef](#)]
68. Soubry, A.; Hoyo, C.; Butt, C.M.; Fieuws, S.; Price, T.M.; Murphy, S.K.; Stapleton, H.M. Human exposure to flame-retardants is associated with aberrant DNA methylation at imprinted genes in sperm. *Environ. Epigenet* **2017**, *3*, dxv003. [[CrossRef](#)]
69. Canbaz, D.; van Velzen, M.J.M.; Hallner, E.; Zwinderman, A.H.; Wickman, M.; Leonards, P.E.G.; van Ree, R.; van Rijt, L.S. Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma. *Indoor Air* **2016**, *26*, 403–413. [[CrossRef](#)]
70. Zhao, F.; Wan, Y.; Zhao, H.; Hu, W.; Mu, D.; Webster, T.F.; Hu, J. Levels of Blood Organophosphorus Flame Retardants and Association with Changes in Human Sphingolipid Homeostasis. *Environ. Sci. Technol.* **2016**, *50*, 8896–8903. [[CrossRef](#)]
71. Araki, A.; Saito, I.; Kanazawa, A.; Morimoto, K.; Nakayama, K.; Shibata, E.; Tanaka, M.; Takigawa, T.; Yoshimura, T.; Chikara, H.; et al. Phosphorus flame retardants in indoor dust and their relation to asthma and allergies of inhabitants. *Indoor Air* **2014**, *24*, 3–15. [[CrossRef](#)]
72. Meeker, J.D.; Cooper, E.M.; Stapleton, H.M.; Hauser, R. Urinary Metabolites of Organophosphate Flame Retardants: Temporal Variability and Correlations with House Dust Concentrations. *Environ. Health Perspect.* **2013**, *121*, 580–585. [[CrossRef](#)]
73. Kanazawa, A.; Saito, I.; Araki, A.; Takeda, M.; Ma, M.; Saijo, Y.; Kishi, R. Association between indoor exposure to semi-volatile organic compounds and building-related symptoms among the occupants of residential dwellings. *Indoor Air* **2010**, *20*, 72–84. [[CrossRef](#)]
74. Meeker, J.D.; Johnson, P.I.; Camann, D.; Hauser, R. Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men. *Sci. Total Environ.* **2009**, *407*, 3425–3429. [[CrossRef](#)]

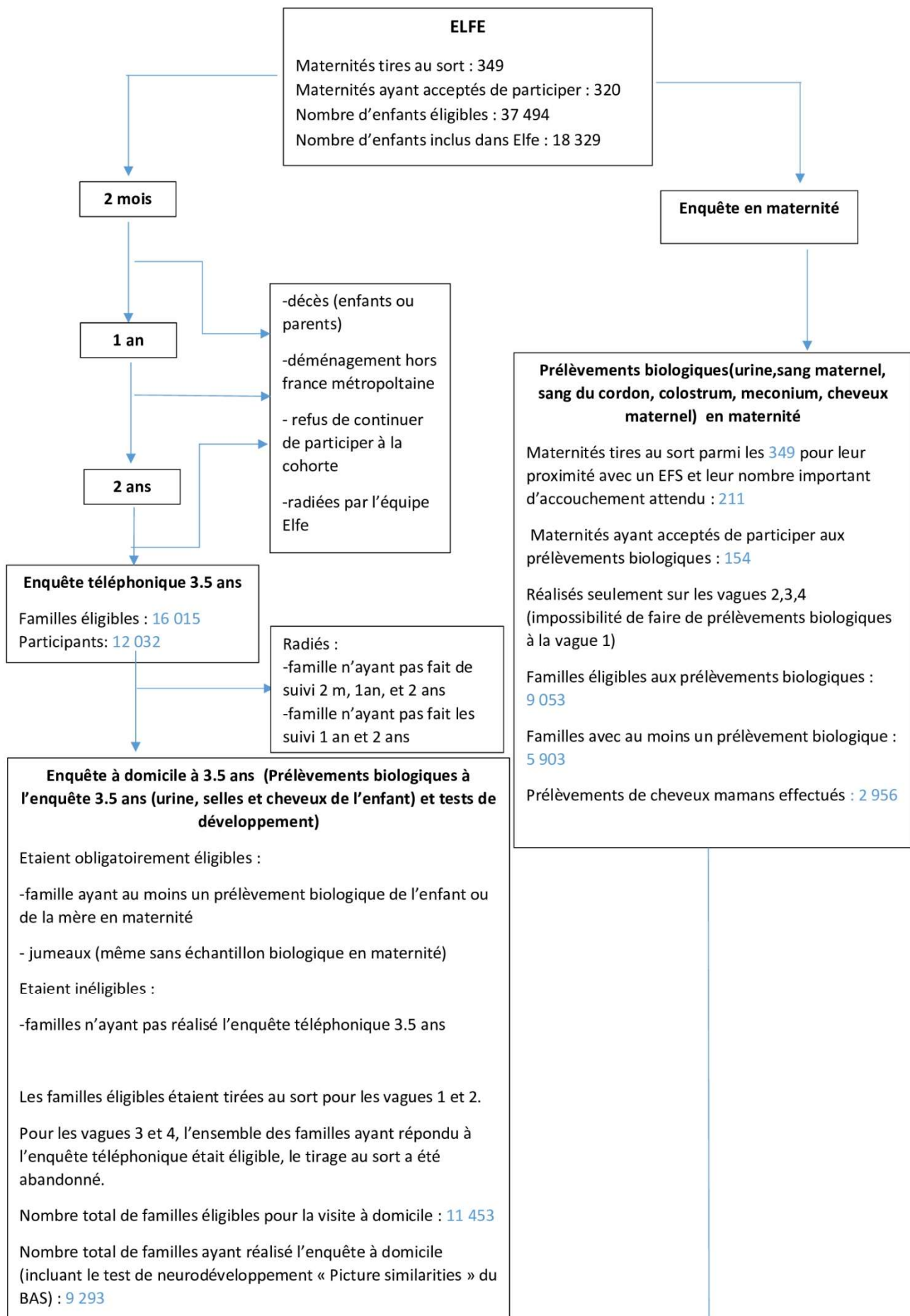


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CHAPITRE 2 : Exposition pré- et post-natale des enfants aux RFOP et ses déterminants dans la population générale, en France.

2. Exposition pré- et post- natale des enfants aux RFOP et ses déterminants dans la population générale, en France

Après avoir réalisé un état de l'art sur les données existantes concernant les RFOP, nous avons décrit l'exposition pré- et post-natale des enfants aux RFOP en France, et explorer les déterminants possibles de ces expositions. 259 enfants et 388 mamans de la cohorte Elfe ont été inclus dans nos analyses. Elfe est une cohorte mère-enfant constituée en France dont l'inclusion a débuté en 2011 et qui a pour but d'étudier les déterminants du développement, de la santé et de la socialisation des enfants, de la naissance à l'adolescence. L'exposition pré- et post-natale des enfants a été estimée grâce aux concentrations en RFOP mesurées dans les cheveux des mamans collectés à la naissance en 2011 et de leurs enfants à 3.5 ans collectés en 2014-2015 pour 15 RFOP. Toutes les analyses ont été pondérées afin d'extrapoler les résultats à l'ensemble des naissances françaises en 2011. Des poids de sondage à chaque temps d'enquête ont été créés par l'équipe Elfe et sont disponibles. Ils permettent de pondérer les analyses réalisées sur les données de la cohorte pour que les résultats soient extrapolables à la population cible de Elfe. La présence de ces poids permet à la cohorte d'être représentative des naissances françaises en 2011. Cependant, dans notre étude, nous utilisons qu'un sous-échantillon des individus inclus dans Elfe. Il était donc impossible d'utiliser en l'état les poids disponibles. Nous avons donc procédé à une correction de ces poids. Cette correction s'est déroulée en deux grandes étapes : une première étape de création de groupes homogènes de réponse (GHR) qui attribue à chaque individu une probabilité d'inclusion dans notre sous-échantillon et une seconde étape de calage. Ce procédé est inspiré de la méthode utilisée par l'équipe Elfe pour la création des poids. La description de la méthode est disponible en ligne (Siméon, 2019). Afin de réaliser les GHR, nous avons, dans un premier temps, détaillé le processus de sélection de nos sous-échantillons (figure 5).



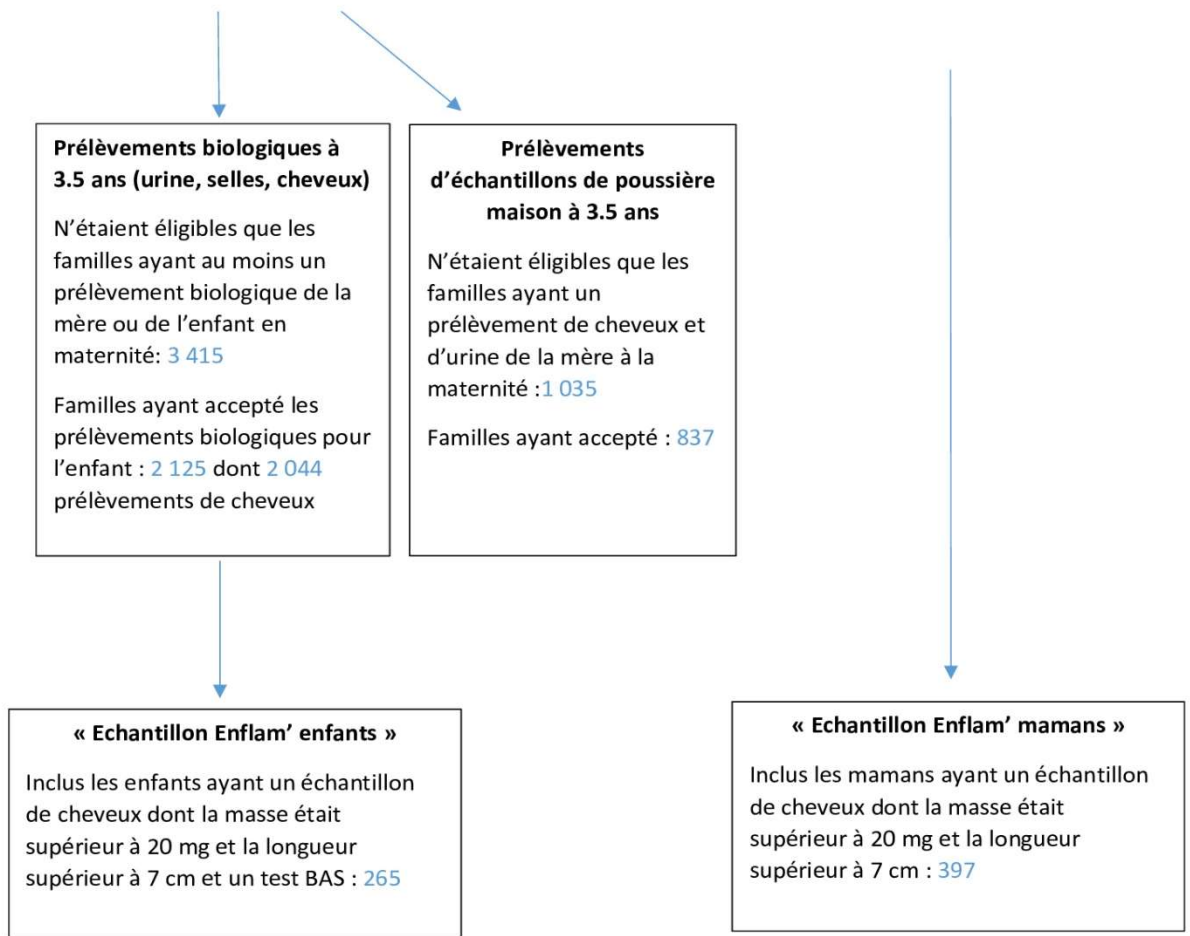


Figure 5. Processus de sélection des échantillons de cheveux des enfants et des mamans.

Cela nous a permis, ensuite, de lister l'ensemble des variables susceptibles d'être associées à la probabilité qu'un individu soit inclus dans nos sous-échantillons. Les variables susceptibles d'être associées à la probabilité qu'un enfant de la cohorte Elfe soit inclus dans notre sous-échantillon sont les suivantes (20 variables) : la région de vie de la mère, la primiparité, l'état matrimonial de la mère à l'accouchement, le niveau d'étude de la mère à l'accouchement, le statut immigré de la mère, la réalisation de séances de préparation à l'accouchement, l'activité du père à l'accouchement, l'âge du père à l'accouchement, la mère vivant en couple ou non à l'accouchement, la consommation d'alcool pendant la grossesse, l'activité professionnelle de la mère à l'accouchement, la vague de l'étude, la nationalité du père, le sexe de l'enfant, l'âge de l'enfant lors du test à 3.5 ans, le prélèvement d'au moins un

échantillon biologique maman ou enfant à la maternité, le niveau d'étude du père à l'enquête 3.5 ans et le niveau d'étude de la mère à 3.5 ans. La liste des variables susceptibles d'être associées à la probabilité qu'une maman soit inclus dans notre sous-échantillon est identique après exclusion des variables du niveau d'étude du père et de la mère à 3.5 ans. Parmi ces variables, nous avons sélectionné celles qui étaient associées significativement à la probabilité d'être inclus dans notre étude par régression logistique. Puis, nous avons testé la corrélation 2 à 2 des variables sélectionnées grâce au « V de cramer » et nous avons gardé les deux variables le moins corrélées entre elles. Le croisement des modalités de ces variables permettait d'obtenir les GHR. À chaque GHR est associé une probabilité qui est identique à tous les individus d'un même GHR. Les cheveux des mamans et des enfants n'ayant pas été collectés au même temps d'enquêtes, des poids différents ont été utilisés pour pondérer l'estimation des exposition pré- et post-natales. 9 RFOP ont été détectés dans plus de 20 % des échantillons. Les moyennes géométriques les plus élevées pour l'exposition prénatale étaient de 272 ng/g pour le TCPP, 69.7 ng/g pour le TPHP et de 54.4 ng/g pour le TDCPP. Les moyennes géométriques les plus élevées pour l'exposition postnatale étaient de 249.6 ng/g pour le TCPP, 85.3 ng/g pour le TDCPP et de 83.8 ng/g pour le ethylhexyldiphényl phosphate (EHDPP). Nous avons observé des corrélations entre les expositions prénatales et entre les expositions postnatales, mais nous n'avons pas observé de corrélations entre les expositions pré- et postnatales pour un même RFOP. L'exposition prénatale à 9 RFOP était associée au polybrominated diphenyl ethers 209 (BDE 209) et 47 (BDE 47). L'IMC pré-grossesse était associé à l'exposition prénatale de tous les RFOP sauf au TBEP. La réalisation de travaux de rénovation dans l'année précédant la naissance de l'enfant était associée à l'exposition prénatale de 6 RFOP. Les déterminants des expositions postnatales semblent être plus disparates avec le type de sol de la chambre de l'enfant associé à l'exposition postnatale de 4 RFOP, de même pour l'exposition postnatale au BDE 47. Enfin, un statut socio-économique plus élevé est associé à de plus faibles expositions à plusieurs RFOP.



Full length article



Pre- and post-natal exposure of children to organophosphate flame retardants: A nationwide survey in France

Z. Chupeau^a, F. Mercier^a, E. Rouxel^a, B. Le Bot^a, G. Chauvet^b, T. Siméon^c, N. Bonvallot^a, C. Zaros^c, C. Chevrier^a, P. Glorennec^{a,*}

^a Univ Rennes, EHESP, Inserm, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, France

^b Ensai (Irmar), Campus de Ker Lann, Bruz, France

^c UM Ined-Inserm-EFS, France

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ABSTRACT

The use of organophosphate flame retardants (OPFRs) has been on the rise ever since many brominated flame retardants were banned, back in the 2000 s. The objectives of this study are to describe the pre- and post-natal exposure of children to OPFRs, and to explore their possible determinants. A total of 259 children aged 3.5 years and 388 mothers from the French ELFE mother–child cohort were included. Both pre- and post-natal exposure to OPFRs were assessed, using OPFR concentrations in the hair of pregnant women (in 2011) and their 3.5-year-old children (in 2014–2015) for 15 OPFRs, of which 9 were detected in > 20 % hair samples. The highest geometric means for pre-natal exposure were 272 ng/g for tris(1-chloro-2-propyl) phosphate (TCPP), 69.7 ng/g for ng/g for triphenyl phosphate (TPP) and 54.4 ng/g for tris(1,3-dichloro-2-propyl) phosphate (TDCPP). The highest geometric means for post-natal exposure were 249.6 ng/g for TCPP, 85.3 ng/g for TDCPP and 83.8 ng/g for 2-ethyl-hexyl diphenyl phosphate (EHDPP). Correlations were found between both pre-natal exposures, and between pre-and post-natal exposures. No correlation was however found between pre-and post-natal exposures for any given OPFR. Pre-natal exposure to the 9 OPFRs was associated with pre-natal exposure to polybrominated diphenyl ethers 209 (BDE₂₀₉), and 47 (BDE₄₇). Maternal BMI was associated with pre-natal exposure to OPFRs other than TBEP. Home renovation work prior to birth was also associated with pre-natal exposure to OPFRs, with the exception of EHDPP, tris(2-butoxyethyl) phosphate (TBEP) and triethyl phosphate (TEP). Determinants of post-natal exposure appeared more disparate across OPFRs; although both the type of flooring in children's rooms and pre-natal exposure to polybrominated diphenyl ethers seem to be associated with post-natal exposure. Lastly, higher socioeconomic status appeared to be associated with lower exposure for several (though not all) OPFRs.

The high prevalence of exposure to OPFRs suggests the need for studies to assess the health effects of OPFRs exposure, particularly on children.

1. Introduction

Organophosphorus flame retardants (OPFRs) are chemical compounds belonging to the organophosphate esters (OPE) chemical class that are added to many consumer products during the manufacturing process (Kemmllein et al., 2003; Van der Veen and de Boer, 2012). In 1992, worldwide usage of flame retardants was estimated at 600,000 t, of which 102,000 t (or about 17 %) were organophosphate-based (Hartmann et al., 2004). Since the 2000 s, these have increasingly been used to replace polybrominated diphenyl ethers (PBDE), a family

of brominated flame retardants classified under the Stockholm Convention as persistent organic pollutants (POPs), and gradually banned (Blum et al., 2019; Chupeau et al., 2020; Stapleton et al., 2012). In 2019, worldwide consumption of flame retardants amounted to >2.39 million tons, 18 % of which were organophosphorous (www.flame-retardants-online.com, 2022). OPFRs were already widely used, (even before the BFR restrictions) and their applications go beyond those of the flame retardants (e.g., as plasticizers) that contribute to the ubiquity of organophosphate esters in products and materials (Hartmann et al., 2004; Patisaul et al., 2021; Sheldon and Hites, 1978; Staaf and Östman,

* Corresponding author

E-mail address: philippe.glorennec@ehesp.fr (P. Glorennec).

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2005). Halogenated OPFRs are mostly used as flame retardants, with the intention of either minimizing the risk of a fire starting, or reducing the spread of fire (European Flame Retardants Van der Veen and de Boer, 2012; European Flame Retardant Association, 2007), while non-halogenated OPFRs are mostly used as plasticizers. OPFRs are widely used in cars, electronics, construction materials, furniture, nail polishes, and textiles (Andresen et al., 2004; Blum et al., 2019; Patisaul et al., 2021; Stapleton et al., 2009; Van der Veen and de Boer, 2012). OPFRs are not chemically bound in products and can be released into the environment via volatilisation, leaching and/or abrasion. Thus, they can be found in biota, sediment, soil and water, as well as in indoor environments (especially dwellings), where people spend the vast majority of their time (Chupeau et al., 2020; Pantelaki and Voutsas, 2021; Van der Veen and de Boer, 2012; Wei et al., 2015). A large prevalence of exposure to OPFRs can thus be expected, including among pregnant women and children. Since OPFRs are semi-volatile, they are regularly found in household air and dust, especially in Europe (Ballesteros-Gómez et al., 2016; Bergh et al., 2011; Björnsdotter et al., 2018; Cequier et al., 2014a; Chupeau et al., 2020; Coelho et al., 2016; Harrad et al., 2016; Langer et al., 2016; Persson et al., 2018; Sugeng et al., 2017; Vykoukalová et al., 2017; Wong et al., 2018; Zhou et al., 2017), and people can thus be exposed by inhalation, skin contact, or dust ingestion (Cequier et al., 2015; Hoffman et al., 2015). Studies on rodents have found that OPFRs are neurotoxic via non-cholinergic pathways, including disruption of both glutamate and gamma-aminobutyric acid (GABA) and of the endocrine system, whereas organophosphorus pesticides do seem to be neurotoxic via cholinergic pathways (Patisaul et al., 2021). Because they may be exposed to OPFRs during a critical period of development (such as in utero and during the first years of life, as reviewed by Chupeau et al., 2020), this raises the question of the health effects of OPFRs on children. Thanks to recent analytic progress and its advantages in considering all sources and routes of exposure, chemical measurement of human biological samples is an increasingly popular tool used in assessing human exposure. Previous European studies have found OPFRs and their metabolites in human biological matrices such as: breast milk (Beser et al., 2019; Sundkvist et al., 2010), urine (Cequier et al., 2015, 2014b; Fromme et al., 2014; Reemtsma et al., 2011; Schindler et al., 2009; Van den Eede et al., 2013; Völkel et al., 2018) and hair (Kucharska et al., 2015a). Human hair analysis is both non-invasive and has the advantages of offering simple and cost-effective sampling, transport and storage as well as sample stability, access to temporal exposure patterns by segmental analysis, and information on short- to long-term exposure to several environmental contaminants (Esteban and Castaño, 2009). Because the hair root is irrigated with blood vessels, chemical contaminants present in the blood stream are incorporated into the internal structure of hair during hair synthesis in the scalp. Exposure information stored in hair is thus very stable over time, and analysis of a 1 cm length of hair is enough to assess average exposure over a 1-month period (Hajeb et al., 2022). Hair is a promising biological matrix for assessing chronic exposure, and thanks to the increased sensitivity provided by the newest analytical systems (Kucharska et al., 2015a, 2015b; Martinez et al., 2021; Peng et al., 2021; Tang et al., 2021; Zhao et al., 2021), is now accessible for organic contaminants (including OPFRs). Hair is thus beginning to be used in epidemiologic surveys, especially for flame retardants (Poon et al., 2018). Because of the relatively short biological half-lives of organophosphate esters, their urinary metabolite concentrations reflect short-term exposure, while OPE levels in hair better reflect long-term exposure because of the low metabolic activities of organophosphate esters in these matrices (Yang et al., 2022).

The aims of this study are to estimate both prevalence and levels of pre- and post-natal exposure to OPFRs in children in France, using OPFR concentrations found in the hair of pregnant women and their 3.5-year-old children respectively, and to explore the role of sociodemographic characteristics, residential building characteristics, and co-exposures to PBDEs as determinants of exposure.

2. Material and methods

2.1. Population

ELFE (Etude longitudinale française depuis l'enfance) is a French national birth cohort. Its objective is to study determinants of the development, health and socialisation of children from birth to adulthood, using a multidisciplinary approach. A total of 349 maternity units (from private or public hospitals) were randomly selected from across metropolitan France, and the children were recruited at birth from the 320 maternity units that agreed to participate. Recruitment took place during 25 days in 2011, grouped into four periods over the year (April 1 – April 4, June 27 – July 4, September 27 – October 4 and November 28 – December 5). Inclusion criteria were single or twin live births at ≥ 33 weeks of gestation, mother ≥ 18 years old with no plans to leave metropolitan France within 3 years, and informed consent signed by either both parents or just the mother, with the father being informed of his right to deny consent for participation (Charles et al., 2020). A total of 18,329 mother–child pairs were recruited.

Biological samples, including hair, were collected from women at birth, at a subsample of 154 maternity units (of 211 that were eligible). These maternity units were selected for their expected number of deliveries (average > 500 deliveries per year) and their proximity (< 150 km) to the biological treatment and storage units made available by the French blood agency. Biological samples were available for women included during the last three periods of recruitment (from June to December in 2011). 2,956 maternal hair samples were collected. These hair samples were cut with scissors in the occipital region (behind the head), at the hairline. The hair strand was attached by paper clip to a cardboard sheet placed in an envelope at room temperature. Data concerning socio-demographic status, family life, parental health, behaviour and life values were collected in the course of a face-to-face interview at birth (Charles et al., 2020).

When the children were 3.5 years old, data concerning day care and school as well as child environmental exposures were collected via telephone interview. For 9,293 children, home visits were specifically organised at this stage of follow-up, to assess the children's cognitive function. Non-invasive biological samples (including hair) were collected from 2,044 children for whom maternal biological samples had already been collected at birth. In families for which both maternal urine and hair samples at inclusion were available, we also obtained a home dust sample (Charles et al., 2020). A total of 74 dust samples were available for our analyses.

Hair strands from mothers and children were cut as close as possible to the scalp, using an identical procedure, before being placed in individual envelopes and shipped to the biobank for storage at ambient temperature (Béranger et al., 2018).

Assuming a hair growth rate of 1 cm per month, we selected all women who had a length of hair strand > 7 cm and a mass of hair strand greater than or equal to 25 mg to ensure detection, and where a British Ability Scale (BAS) Picture Similarities test was available for her child ($n = 397$), in anticipation of a future epidemiological study. OPFR concentration in the first 7 cm (proximal) from maternal hair samples allowed estimation of integrated exposure during the 7 months of pregnancy known as pre-natal exposure. Their children were included if the child's hair strand was greater than or equal to 25 mg ($n = 265$). Post-natal exposure was estimated by the OPFR concentration measured from these hair samples. We excluded seven mothers and three children for whom there was no concentration available for at least one chemical. We also excluded 2 mothers and three children for whom statistical weight was not available at birth and at 3.5 years, respectively. In the end, our sample comprised 388 mothers and 259 children (Fig. 1). During the home visit at 3.5 years dust samples were collected by the investigator (from the vacuum cleaner and the floor of the room where the child played most often). These were placed in a zipped bag and then in a black bag for protection from light (Blanchard et al., 2014; Charles

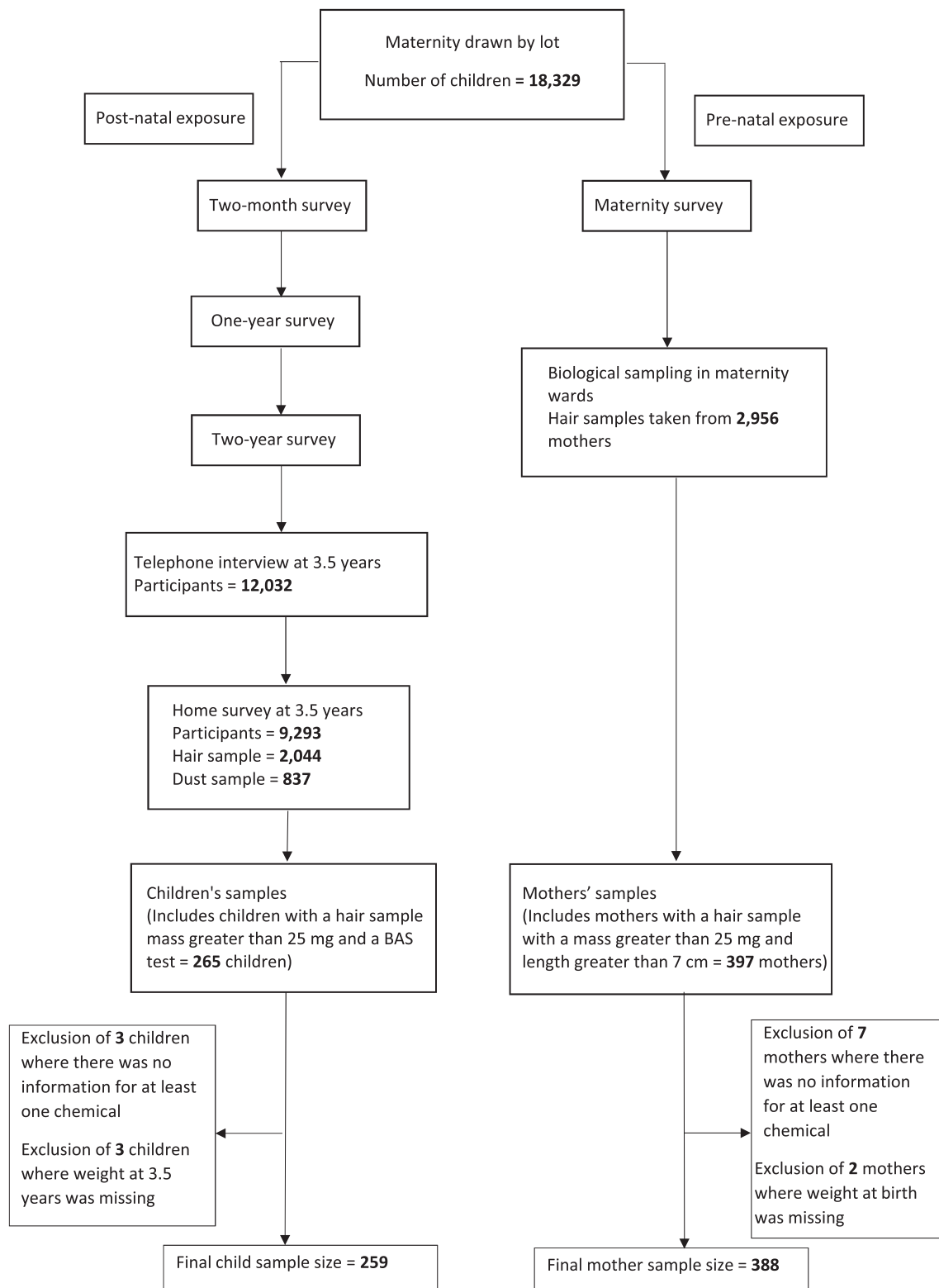


Fig. 1. Mother and child recruitment in the ELFE cohort, for evaluation of pre- and post-natal exposure.

et al., 2020). Of the 74 dust samples available for our study participants, 50 were randomly selected.

2.2. Choice of OPFRs of interest and choice of other flame retardants

The OPFRs were prioritised according to European production (or import tonnage) and their chemical properties facilitating exposure; of

the top-ranking chemicals (Niang et al., 2019), fifteen were measured simultaneously: diethyl ethyl phosphonate (DEEP), ethylhexyl diphenyl phosphate (EHDPP), tris(2-butoxyethyl) phosphate (TBEP), tri-*n*-butyl phosphate (TBP), tris(2-chloroethyl) phosphate (TCEP), tris(2-chloropropyl) phosphate (TCPP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), tris(2-ethylhexyl) phosphate (TEHP), triethyl phosphate (TEP), tri-*m*-cresyl phosphate (TMCP), trimethyl phosphate (TMP), tri-

o-cresyl phosphate (TOCP), tri-isopropyl phosphate (TIPP), triphenyl phosphate (TPP) and trixylenyl phosphate (TXP). To study potential co-exposures to other flame retardants, eight PBDEs (BDE 28, 47, 85, 99, 100, 119, 153 and 154) were also measured in these same hair samples from mothers and children, as well as in dust. BDE₂₀₉ was also measured in maternal hair samples, though not (for economic reasons) in children's hair samples.

2.3. Chemical analyses

Hair and dust samples were analysed by the LERES (Laboratory for Study and Research into the Environment and Health) at the French School of Public Health (EHESP, Rennes, France). A detailed description of the analytical methods used (including quality assurance and quality control) is available elsewhere (Yon et al., 2022) and is briefly described below.

Approximately 30 to 50 mg of each (unwashed) hair sample was accurately weighed and transferred to a 5 mL stainless steel grinding jar, using one 10 mm ball per jar. Grinding was performed in the mixer mill MM400 (Retsch GmbH, Haan, Germany) for 10 min at 25 Hz. The resulting hair powder was transferred into an amber glass vial, which was then sealed and stored at -18°C until the time of chemical analysis.

Dust was passed through a pre-cleaned (dichloromethane) 250 μm stainless steel sieve using a Retsch AS 200 vibratory sieve shaker (Retsch GmbH, Haan, Germany) to remove coarse material (cotton and debris). The sieved dust was then stored at -18°C in a hermetically sealed 20 mL amber glass flask until the time of chemical analysis.

Target chemicals were extracted from the hair and settled dust samples using a pressurised liquid extractor (PLE) ASE (Accelerated Solvent Extractor) 350 (Dionex Corporation, Sunnyvale, USA). This procedure was adapted from a previous study (Mercier et al., 2014). Briefly, 20–25 mg of hair powder or settled dust was accurately weighed and mixed with 2.4 g of pre-conditioned Celite® 545. The mixture was then loaded into a 5 mL stainless steel extraction cell. After the addition of internal standards (ISTDs), the extraction process was performed with dichloromethane, then repeated once using fresh solvent. The two organic extracts were combined, transferred into clean glass tubes and concentrated to 0.5 mL at 30°C under a nitrogen stream, using a N-EVAP 111 Organomation Nitrogen Evaporators. Concentrated extracts were transferred into 1.5 mL amber glass vials (with aluminium caps fitted) with a PTFE/silicon/PTFE septum, and stored at -18°C prior to analysis by GC/MS/MS. Analyses were performed using a 7890B GC system coupled to a 7010B GC/MS Triple Quad (Agilent Technologies, Santa Clara, California, United States) operated in electron impact ionization (EI) mode (70 eV). The GC system was equipped with a 7693 Autosampler and a split/splitless (SSL) injector fitted with a 4.0-mm I.D. single taper borosilicate glass liner with deactivated wool (Siltek deactivation) supplied by Restek Corporation (Bellefonte, Pennsylvania, United States). Calibration samples and sample extracts were injected (1 μL) in the splitless mode (250°C). Helium was used as the column carrier gas, at a constant flow rate of 1.0 mL/min. Chromatographic separation was performed on an Rtx®-PCB capillary column (30 m length \times 0.25 mm I.D., 0.25 μm film thickness) supplied by Restek Corporation (Bellefonte, Pennsylvania, United States), using the following oven temperature programme: 37°C (hold 1.85 min), first ramp at $30^{\circ}\text{C}/\text{min}$ to 250°C (hold 8.5 min), second ramp at $20^{\circ}\text{C}/\text{min}$ to 320°C (hold 8 min to reach an analysis time of 28.95 min). The MSD transfer line, ion sources and quadrupole temperatures were fixed at 315, 270 and 150°C , respectively. The mass spectrometer (triple quadrupole) was operated in multiple reaction monitoring (MRM) mode. The two most intense and specific MRM transitions of each compound (quantifier and qualifier transitions) were monitored for identification, confirmation and quantification.

2.4. Selection of potential exposure determinants

Potential determinants of OPFRs exposure were chosen, a priori, on the basis of the literature. Some are related to socioeconomic and health status: parental education level, household income, BMI (Doherty et al., 2019), number of people living in the dwelling (Percy et al., 2020). Some are related to the building, such as construction date (Canbaz et al., 2016), flooring material and aeration (Araki et al., 2014). A further criterion was data availability in the ELFE survey. (Araki et al., 2014; Brommer et al., 2012; Canbaz et al., 2016; Carignan et al., 2018; Castorina et al., 2017; Cequier et al., 2015; Coelho et al., 2016; Deziel et al., 2018; Hoffman et al., 2017; Larsson et al., 2018; Meeker et al., 2013; Soubry et al., 2017; Sugeng et al., 2017; Wong et al., 2018; Zheng et al., 2017). Finally, concerning potential sources of OPFRs exposure and co-exposures, six variables were built: renovation work in dwelling in the past year for pre- and post-natal exposure (from either the maternity survey or the 3.5 years survey, respectively), construction year of home, type of floor in child's room and duration of breastfeeding for post-natal exposure, and BDE₄₇, BDE₂₀₉, exposure for pre- and post-natal exposure (BDE₄₇ only). Concerning the potential health and socio-demographic determinants for both pre- and post-natal exposures, we used maternal education level, household income, number of persons living in the home and pre-pregnancy maternal BMI. For post-natal exposure, we were also able to consider lifestyle determinants and housing characteristics: time spent outside by the child, time spent by the child using electronic devices, number of windows in the child's room, ventilation in the child's room. We also considered season of sampling.

2.5. Statistical analyses

The ELFE cohort is based on a two-stage random stratified sampling design (stratified for maternity units and for selected days). Initial weights from ELFE cohort sampling and correction for unit non-response at baseline were available for both the maternity surveys (pre-natal exposures) and the 3.5 year surveys (post-natal exposures).

The weighting process comprised three steps. First, we created Response Homogeneity Groups (RHGs) to reduce non-response bias. We obtained each participant's probability of inclusion in our study. The inverse of this probability was then multiplied by the initial weight from ELFE cohort sampling. These weights were calibrated to reduce the variance of estimators. Second with respect to the French population, using the margins of the National Perinatal Survey (Blondel and Kermarrec, 2011). All of the following results were weighted, with the exception of correlations between OPFR levels in children's hair and house dust. The number of dust samples was too small to compute weighted correlations and obtain results for the French population. The unweighted results are available in the [supplementary materials](#).

Potential determinants had low missing data, with the exception of year of house construction information (collected at the maternity survey, for pre-natal exposure) which had $>95\%$ of missing data and was therefore not included in our analyses. The type of flooring in the child's room was the variable with the highest percentage of missing data (8%). Variables with $<5\%$ of missing data were imputed by the mode. Variables (maternal education level, household income, construction year of house (collected at 3.5 years), type of floor in the child's room) with missing data $>5\%$ and $<8\%$ were imputed using prediction via logistic regression with the two most-correlated other variables.

Left-censored OPFR concentrations measured in dust and hair samples (up to 80 % of censored data) were imputed (Helsel, 2011); those with $>80\%$ of censored data were considered for data description only, rather than for correlations nor determinants analysis. For each chemical, we used the maximum-likelihood estimation method (MLE) to estimate parameters of lognormal probability distribution (Helsel, 2011). Then, for each LOD in each chemical, censored data were imputed by random values between 0 and the LOD from this estimated distribution

(Jin et al., 2011). This method allowed us to take into account the presence of multiple LODs in each chemical.

The geometric mean and geometric standard deviation and median (2nd quartile), 1st and 3rd quartile were calculated. Since these were not (according to the Shapiro-wilk test) distributed normally, OPFR concentrations in hair and dust were log-transformed to ensure normality. Correlations between OPFR concentrations in each population and between mother-child pair levels were assessed using Pearson's correlation matrices. Correlations between OPFR concentrations in children's hair and house dust were also analysed using Pearson's correlation.

Linear associations between log-transformed hair concentrations and potential determinants were tested using univariates analysis.

SAS software 9.4 was used to impute censored data and describe OPFR concentrations. The CALMAR macro available in SAS software 9.4 was used for calibration (Deville et al., 1993). Weighted results were calculated using the SURVEY package from R software V4.0.

2.6. Ethical issues

Ethical approvals for data collection in maternity units, and for each data collection wave during follow-up, were obtained from the French national advisory committee on information processing in health research (CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé), the French national data protection authority (CNIL: Commission Nationale Informatique et Liberté) and, in the case of invasive data collection (such as biological sampling) the committee for the protection of persons engaged in research (CPP: Comité de Protection des Personnes). The ELFE study was also approved by the national committee for statistical information (CNIS: Conseil National de l'Information Statistique) (Charles et al., 2020).

Table 1

Characteristics of pregnant women and children included in our study, and in the French population in 2011*.

Determinants	Modalities	Study sample (unweighted results) (%)		France (weighted results) (%)	
		Mother-child pairs (n = 259)	Mothers (n = 388)	Mother-child pairs	Population of Mothers
Sex of child^b	Boy	40.9	53.6	44.1	49.8
	Girl	59.1	46.4	55.9	50.2
Mother's age^{a b}	NA (%)	1.1	0	1.1	0
	25–30	18.5	43.5	24.8	45.8
	31–35	38.7	34.8	40.1	34.0
	36–40	30.1	17.8	24.2	15.6
	>40	12.7	3.9	10.9	4.6
Mother's BMI^b	NA (%)	0.8	0	0.7	0
	<18.5	6.9	8.2	4.4	8.9
	18.5 - < 25	70.7	69.1	69.1	62.0
		15.1	14.7	12.5	12.7
	25 - < 30	7.3	8.0	14.0	16.3
Mother's education level^{a b}	30 or more	0.8	1	0.7	1
	NA (%)				
	<= BAC	23.6	26.5	44.3	46.1
	BAC + 2	23.1	26.3	16.6	18.8
	> BAC + 2	53.3	47.2	39.1	35.1
Father's education level^{a b}	NA (%)	0.8	0.8	0.7	0.8
	<= BAC	42.5	43.5	61.6	58.0
	BAC + 2	20.8	20.4	16.7	15.7
	> BAC + 2	36.7	36.1	21.7	26.3
	NA (%)	3.1	5	3	5
Monthly household Income (euros)^{a b}	<=2,999	22.8	33.5	39.0	52.9
	[3,000; 3,999]	27.4	31.2	27.3	22.7
	>= 4,000	49.8	35.3	33.7	24.1
	NA (%)	4.5	5.5	4.6	5.5
	>= 4,000	49.8	35.3	33.7	24.1
Smoking status during pregnancy^b	Not a smoker	80.7	82.2	75.9	78.8
	Smoker	19.3	17.8	24.1	21.2
	NA (%)	0.3	0.8	0.7	0.8
Alcohol consumption during pregnancy^b	No	72.9	75.3	80.0	79.1
	Yes	27.1	24.7	20.0	20.9
	NA (%)	0.8	0.3	0.3	0.3
Duration of breastfeeding (months)^a	<= 1	37	X	36.8	X
] 1; 4]	30.9		27.7	
	>4	32.1		35.5	
	NA (%)	0.08		0.1	
Season when hair was collected^{ab}	Summer	0	31.44	0	31.9
	Autumn	33.2	68.6	37.7	68.1
	Winter	66.8	0	62.3	0
	Spring	0	0	0	0
	NA (%)	1.9	3.4	1.9	3.4
Number of people in household^{ab}	<= 3 people	24.3	44.3	27.7	45.7
	4 people	48.6	37.4	41.6	36.2
	>5 people	27.1	18.3	30.7	18.1
	NA (%)	0.08	3.4	0.1	3.4

*: Excluding French overseas territories.

N: number; SD: standard deviation; NA: percentage of missing data for 383 mothers and 259 children; ^a variables present in the 3.5-year questionnaire; ^b variables present in the maternity questionnaire or in the two-month questionnaire; x: data not collected in either the maternity survey or the 2-month survey; the percentages of the modalities exclude NA.

3. Results

3.1. Population

Characteristics of mothers (for pre-natal exposures) and children (for post-natal exposures) are presented in [Table 1](#), with unweighted and weighted estimations. Unweighted results describe the participants included in our analyses (388 mothers and 259 children). Weighted results describe the entire population of women who gave birth in France in 2011, and their children at 3.5 years. The population of mothers and the population of mother–child dyads differed in terms of several sociodemographic characteristics: mothers among the population of the mother–child dyads were older and better-educated than the population of mothers. The population of the mother–child dyads group was also characterized by higher household income per month and a higher number of persons in the household. For other characteristics listed in [Table 1](#), differences were fewer. In the population of mothers, mean age at inclusion was 31 years (standard deviation: 0.5). During pregnancy, 79 % of French mothers did not smoke, 79 % did not drink alcohol and 16 % were obese (BMI \geq 30 kg/m²) before the pregnancy in question. For more than half of the fathers, educational attainment was below degree level, and for 53 % of families, monthly household income was <2,999 euros. A slightly higher proportion of girls was observed (50.2 % vs 49.8 %) among the children.

3.2. Pre- and post-natal exposure to OPFRs

Pre- and post-natal exposure to OPFRs are presented in [Table 2](#), while unweighted results are presented in [Table S2](#). For pre-natal exposure, TMP was not detected. Five OPFRs (DEEP, TEHP, TiPP, TOCP and TXP) were detected in < 5 % of hair samples. EHDPP, TBEP, TBP, TCEP, TCPP, TDCPP, TEP, TMCP and TPP were detected in > 20 % of hair samples. For post-natal exposure, TXP was not detected, five OPFRs (DEEP, TEHP, TiPP, TOCP and TMP) were detected in < 5 % of

hair samples. EHDPP, TBEP, TBP, TCEP, TCPP, TDCPP, TEP, TMCP and TPP were detected in > 20 % of hair samples; their concentrations were imputed and used in later analyses. The highest geometric mean was measured for TCPP in both pre-natal (geometric mean: 272 ng/g, IC95%: 269; 274) and post-natal (geometric mean: 250 ng/g; IC 95 %: 247; 252) exposure. The highest concentration was observed for TCPP with P₉₅: 822 and 631 ng/g for pre- and post-natal exposures, respectively. There is no clear pattern between post-natal and pre-natal exposures, post-natal being higher for half of the OPFRs (EHDPP, TBEP, TCEP, TDCPP and TPP), and lower for others. Pre- and post-natal PBDE exposures are available in the [supplementary material](#) (Tables S7-8) as well as PCB exposures (Tables S7-8) and correlations ([Fig S8–11](#)).

3.3. Correlations of children's exposure to OPFRs, and OPFR concentration in house dust

[Figs. S1 and S2](#) in the [supplementary material](#) show correlation matrices for OPFRs with a detection rate > 20 % (9 OPFR for pre- and post-natal exposure). Many positive correlations can be observed in the pre-natal correlation matrix. Correlation coefficients range from −0.1 (between TCEP and TEP) to 0.5 (between EHDPP and TPP). Many positive significant (p < 0.5) correlations can be observed for post-natal exposure, with no negative correlations, up to 0.45 (between TCPP and TPP). [Fig. S3](#) presents OPFR correlations between pre- and post-natal exposure. Some weak correlations were observed (from −0.2 for TBP to 0.26 for TCPP). As displayed in [Fig. S7](#), the only post-natal exposure significantly correlated to OPFR dust concentration was TEP, with very weak association (r = −0.02, p.value < 0.05).

3.4. OPFR exposure determinants

The associations between children's pre- and post-natal exposure to OPFRs, and their potential determinants, are shown in [Table 3](#) and [Table 4](#). Relationships (β) are for (log)transformed concentrations.

Table 2

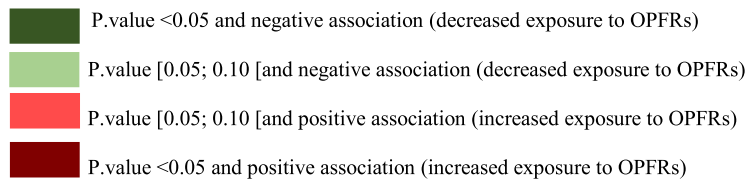
Pre- and post-natal exposure of children to OPFR, measured by concentrations (ng/g) in mothers' hair at birth in 2011 and in the hair of children aged 3.5 years old in 2014–2015, in France.

OPFR	CAS number	Populations	% > LOD	Min	P25	P50	P75	P95	Max	Geometric mean [IC95%]
EHDPP	1241-94-7	Children	95	11	40	73	204	244	4,423	83.7 [81.6; 85.9]
		Mothers	92.2	0.7	22	35	58	182	51,204	39.1 [37.; 41.2]
DEEP	78-38-6	Children	1.9	–	–	–	–	–	–	–
		Mothers	2.9	–	–	–	–	–	–	–
TBEP	78-51-3	Children	49.8	0.8	24	53	116	281	2,082	53.7 [51.5; 56.0]
		Mothers	25.3	31	34	35	37	225	2,034	46.2 [44.6; 48.8]
TBP	126-73-8	Children	45.9	4.5	15	20	26	33	89	20.4 [18.3; 22.4]
		Mothers	92.7	9.5	27	35	45	61	84	34.5 [32.4; 36.5]
TCEP	115-96-8	Children	68.3	0.9	9.2	15	28	49	623	15.6 [13.4; 17.8]
		Mothers	61.3	0.2	7.1	13	23	102	939	14.2 [12; 16.4]
TCPP	13674-84-5	Children	66.4	37	159	246	399	631	11,848	250 [247; 252]
		Mothers	74.7	14	203	260	401	822	3,155	272 [269; 274]
TDCPP	13674-87-8	Children	97.3	3.0	32	79	161	542	2,343	85.3 [83.0; 87.5]
		Mothers	95.3	2.4	23	47	109	456	16,689	54.4 [52.2; 56.6]
TEHP	78-42-2	Children	1.1	–	–	–	–	–	–	–
		Mothers	1.3	–	–	–	–	–	–	–
TEP	78-40-0	Children	67.9	2.3	9.2	13	18	34	153	13.5 [11.4; 15.6]
		Mothers	95.3	4.0	22	49	77	130	238	42.4 [40.3; 44.5]
TiPP	513-02-0	Children	0.4	–	–	–	–	–	–	–
		Mothers	0.5	–	–	–	–	–	–	–
TMCP	563-04-2	Children	38.2	0.1	1.0	3.5	4.4	29	1,229	2.9 [0.6; 5.2]
		Mothers	78.3	0.1	5	10	27	205	18,194	12.8 [10.5; 15.1]
TMP	512-56-1	Children	0.39	–	–	–	–	–	–	–
		Mothers	0	–	–	–	–	–	–	–
TOCP	78-30-8	Children	1.16	–	–	–	–	–	–	–
		Mothers	0.8	–	–	–	–	–	–	–
TPP	115-86-6	Children	100	8.0	44	76	143	242	1,874	77.5 [75.2; 79.5]
		Mothers	99.5	5.4	35	61	106	793	8,621	69.7 [67.5; 71.9]
TXP	25155-23-1	Children	0	–	–	–	–	–	–	–
		Mothers	0.5	–	–	–	–	–	–	–

N.B: Displayed concentrations were imputed when % > LOD was > 20 %.

Table 3
Determinants of children’s pre-natal exposure to OPFR, France (2011).

Determinants	Modalities	EHDPP	TBEP	TBP	TCEP	TCPP	TDCPP	TEP	TMCP	TPP
Home renovation work before birth	No (ref)									
	Yes									
Maternal BDE ₄₇ concentration at birth (ng/g)	≤ 0.43 ng/g (ref)									
]0.43; 1.23]									
	>1.23									
Maternal BDE ₂₀₉ concentration at birth (ng/g)	≤ 5.4 ng/g (ref)									
]5.4; 11.8]									
	>11.8									
Maternal education level at birth	≤ BAC (ref)									
	BAC +2									
	> BAC+2									
Monthly household income at birth (euros)	≤ 2,999 € (ref)									
]3,000; 3,999] €									
	>=4,000 €									
Number of persons in the household at birth	≤ 3 people (ref)									
	4 people									
	>=5 people									
Pre-pregnancy BMI	18.5; 25] (ref)									
	< 18.5									
]25; 30 [
	>30									
Season of maternal hair sampling	Autumn (ref)									
	Summer									



With regard to potential sources of OPFR exposure and co-exposures, renovation work undertaken in the home during the year before birth was associated with a p-value < 5 % and higher pre-natal exposure to TBP ($\beta = 0.08 [0.00; 0.16]$), TCEP ($\beta = 0.37 [0.13; 0.60]$), TCPP ($\beta = 0.15 [0.01; 0.29]$), TDCPP ($\beta = 0.53 [0.26; 0.79]$), TMCP ($\beta = 0.43 [0.09; 0.77]$) and TPP ($\beta = 0.43 [0.22; 0.65]$). This trend was observed for post-natal exposure for TCEP and TDCPP, though without statistical significance. The presence of lino (for TBEP and TPP), carpet (TCEP) or parquet (TBEP, TCPP and TPP) in the child’s room was significantly associated with higher post-natal exposure to some OPFRs (TBEP, TCEP, TCPP and TPP), in comparison with tiles. Year of home construction was not associated with post-natal exposure to OPFRs. Children breastfed for >4 months had lower exposure to TEP ($\beta = -0.26 [-0.47; -0.06]$) than children breastfed for <1 month. Pre-natal exposure to BDE₄₇ (3rd tertile > 1.23 ng/g, vs 1st tertile) was associated with higher pre-natal exposure to TBP ($\beta = 0.18 [0.08; 0.29]$), TCEP ($\beta = 0.42 [0.09; 0.76]$), TCPP ($\beta = 0.43 [0.24; 0.62]$), TEP ($\beta = 0.30 [0.04; 0.50]$), TMCP ($\beta = 1.26 [0.80; 1.72]$) and TPP ($\beta = 0.32 [0.02; 0.63]$). Post-natal exposure to BDE₄₇ (3rd tertile > 1.23 ng/g) was also associated with post-natal exposure to TBP ($\beta = 0.13 [0.01; 0.26]$) and TCPP ($\beta = 0.46 [0.22; 0.71]$), as well as to EHDPP ($\beta = 0.36 [0.03; 0.70]$). Higher pre-natal exposure to BDE₂₀₉ concentration (3rd tertile > 11.8 ng/g, vs 1st tertile) was significantly associated with an increase in all OPFR pre-natal exposure (p.value < 0.05), with the exception of TCPP and TEP.

The highest maternal education level (>high school) was significantly associated with lower pre-natal exposure to EHDPP ($\beta = -0.27 [-0.47; -0.07]$) and post-natal exposure to TDCPP ($\beta = -0.43 [-0.76; -0.10]$) and TEP ($\beta = -0.21 [-0.40; -0.01]$) and with higher pre-natal exposure to TCPP ($\beta = 0.19 [0.03; 0.35]$). The highest household income

(3rd tertile: > 4,000 euros per month) was associated with lower pre-natal exposure to EHDPP ($\beta = -0.40 [-0.60; -0.17]$), TEP ($\beta = -0.36 [-0.56; -0.16]$) and TMCP ($\beta = -0.64 [-1.05; -0.22]$) and lower post-natal exposure to TBP ($\beta = -0.20 [-0.32; -0.09]$), TDCPP ($\beta = -0.49 [-0.84; -0.14]$) and TEP ($\beta = -0.34 [-0.54; -0.13]$). Living in a home with five persons or more was associated with lower pre-natal exposure to TBP ($\beta = -0.19 [-0.29; -0.08]$) but higher EHDPP ($\beta = 0.27 [0.03; 0.52]$) and TBEP ($\beta = 0.20 [0.001; 0.40]$) and lower post-natal exposure to TMCP ($\beta = -0.66 [-1.19; -0.12]$) compared to homes with three persons or less. Pre-pregnancy obesity (vs normality) was significantly associated with higher pre-natal exposure to all OPFRs, though not with TBEP. No such association was observed for post-natal OPFR exposure, other than for TBEP, for which exposure was lower ($\beta = -0.74 [-1.17; -0.31]$).

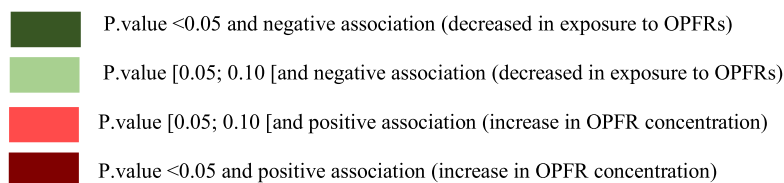
When considering lifestyle determinants and housing characteristics as potential determinants of post-natal exposure, we observed that children spending >4.5 h per week outdoors had higher exposure to TDCPP ($\beta = 0.54 [0.19; 0.90]$) and children using electronic devices between 2 and 4 h per week had lower exposure to TBEP ($\beta = -0.45 [-0.85; -0.04]$), TCEP ($\beta = -0.45 [-0.77; -0.13]$), TDCPP ($\beta = -0.53 [-0.91; -0.15]$) and TPP ($\beta = -0.34 [-0.63; -0.04]$) compared with children spending <2 h per week using electronics devices. This lower exposure to TPP was also observed for children using electronic devices >4 h per week ($\beta = -0.30 [-0.57; -0.04]$).

The presence of two windows (vs one) in the child’s bedroom was associated with higher exposure to TCEP ($\beta = 0.38 [0.03; 0.74]$), as well as presence (vs absence) of ventilation in the bedroom, with higher exposure to TDCPP ($\beta = 0.36 [0.03; 0.69]$).

The summer season (compared to the autumn season) was associated

Table 4
Determinants of children’s post-natal exposure to OPFR, France (2014–2015).

Determinants	Modalities	EHDPP	TBEP	TBP	TCEP	TCPP	TDCPP	TEP	TMCP	TPP
Home renovation work at 3.5 years of child during the year before the survey	No (ref)									
	Yes									
Residential home year construction at 3.5 years of child	> 2000 (ref)									
	[1970; 2000]									
	< 1970									
Type of floor in the children's room	Tiles (ref)									
	Lino									
	Carpet									
	Parquet									
Duration of breastfeeding	<=1 month (ref)									
] 1 ; 4] months									
	>4 months									
Children’s BDE ₄₇ concentration at 3.5 years(ng/g)	<= 0.43 ng/g (ref)									
]0.43; 1.23]									
	>1.23									
Maternal education level at 3.5 years of child	<= BAC (ref)									
	BAC +2									
	> BAC+2									
Monthly household income at 3.5 years of child (euros)	<=2,999 € (ref)									
	[3,000; 3,999] €									
	>=4,000 €									
Number of persons in the household at 3.5 years of child	<=3 people (ref)									
	4 people									
	>=5 people									
Pre-pregnancy BMI	[18.5; 25] (ref)									
	< 18.5									
	[25; 30 [
	>30									
Time spent outside by children at 3.5 years (hours/week)	<=4.5 hours (ref)									
]4.5; 7] hours									
	>7 hours									
Time spent using electronic devices by children at 3.5 years (hours/week)	<=2 hours (ref)									
]2; 4] hours									
	> 4 hours									
Number of windows in child’s room	1 window (ref)									
	2 windows									
Ventilation in child’s room	Yes (ref)									
	No									
Season of children’s hair sampling at 3.5 years	Autumn (ref)									
	Winter (child)									



with either higher pre-natal exposures for EHDPP ($\beta = 0.41$ [0.22; 0.60]), TDCPP ($\beta = 0.30$ [0.02; 0.60]), TEP ($\beta = 0.19$ [0.01; 0.36]) and TMCP ($\beta = 0.44$ [0.07; 0.80]) or with lower pre-natal exposure for TBEP ($\beta = -0.21$ [-0.36; -0.05]. The winter season (compared to the autumn season) was associated with lower post-natal exposure to TDCPP ($\beta = -0.54$ [-0.84; -0.25]) and TPP ($\beta = -0.25$ [-0.48; -0.01]).

4. Discussion

To our knowledge, this is the first study to describe pre- and post-

natal OPFRs exposure in children in France, and finds exposure to several OPFRs to be ubiquitous.

We used OPFR concentrations in the hair of pregnant women and their 3.5-year-old children to estimate exposure. This is a non-invasive matrix, quite easy to collect and store, and reflects several months of exposure, reflecting the content of blood, and thus what the foetus may be exposed to; it has thus been proposed as an indicator of exposure (Kucharska et al., 2015a). A toxicological study on rats has shown that hair can provide a relevant assessment of exposure to contaminants (Appenzeller et al., 2017); these authors demonstrated, using cross-

sectional measurements, that the concentration of pesticides, including those that are organophosphorous, and their metabolites in hair was representative of the level of exposure in the experiments. For all chemicals detected in hair, the association between exposure and concentration in hair was always significant. For most compounds (including organophosphorus pesticides) the association between exposure intensity and the concentration of chemicals in hair was stronger than (or comparable to) that found in urine and plasma (Appenzeller et al., 2017). We are not aware of the existence of such a study for OPFRs. However, certain limitations prevent the wide application of hair as a matrix for human biomonitoring to flame retardants. For instance, only a small amount of hair can be sampled per individual (normally 0.05 to 0.2 g), and in addition, participants may not wish to donate hair. Also, the number of strands and their lengths (from 2 to 10 cm) were not homogeneous between children. Consequently, the hair-measurements of the 3.5-year-old children may reflect various exposure windows from the previous several months to about one year. Furthermore, interpretation of hair levels is not without ambiguity, as they reflect both external exposure (via deposition from air and dust) and internal exposure (through contact with blood at the hair follicle/root). As there is not yet any effective procedure capable of eliminating contamination that is exclusively external (Kucharska et al., 2015a), the hair used in our study was not washed. Distinguishing between these exposure routes can be difficult, especially when hair is used as an indicator of exposure to flame retardants, where the contribution made by atmospheric deposition cannot be ignored (Hajeb et al., 2022). However, (Kucharska et al., 2015a) found very weak or no correlation of OPFR concentrations in mothers' and children's hair and estimated that it indicates that the concentrations measured in the hair of mothers and children are not driven by the (minor) amount of dust deposited onto the hair surface.

A further limitation of the present study concerns censored exposure data. Since our study was exploratory, we decided to impute OPFR concentrations with a percentage of censored data of up to 80 %. However, the weighting process enables us to take the initial (ELFE) sampling design into account. In particular, large maternity units were oversampled, which is accounted for in the initial design weights. The weighting process also enables us to correct for unit non-response at the various steps of the survey. This is performed using the Response Homogeneity Groups method, and leads to a strong reduction of the non-response bias. Lastly, the weights are calibrated on margins from the French National Perinatal survey, which results in reduced variance of estimators. In all, the weighting process is key to describing pre- and post-natal OPFR exposure precisely for the entire population of children born in 2011 in France. Because our objective was descriptive, we did not correct for multiplicity of tests, and neither did we adjust the models.

The final limitation is related to data unavailability for some determinants – because ELFE is a generalist cohort, without any specific focus on flame retardants. Some major determinants, such as number of electronic devices in the household, (Sha et al., 2018) or cleaning frequency, (Canbaz et al., 2016; Cequier et al., 2015; Larsson et al., 2018) could not be studied. Cleaning frequency data was collected, but we decided not to use it because of high levels of missing data (>80 %).

The first strength of our study is the wide exposure period covering pregnancy. The hair root is irrigated by blood vessels, and chemical contaminants present in the blood stream are incorporated into the internal structure of hair during hair synthesis in the scalp. Exposure information stored in hair is very stable over time, and analysis of 1 cm hair length is accepted to assess average exposure over a 1-month period (Hajeb et al., 2022). Considering the human hair growth rate of 1 cm per month, and with a minimal length of 7 cm, we assessed children's OPFR exposure during at least 7 months of pregnancy.

The second strength of our study is that we were able to assess exposure to a wide variety of currently-used OPFRs (nine OPFRs in both the pre-natal and post-natal periods). In a Norwegian mother-child cohort, seven OPFRs were measured in the hair samples of both mothers

(n = 48) and children (n = 54) aged 6–12 years old, (collected simultaneously) between January and mid-May 2012 (Kucharska et al., 2015a). In our study, maternal hair samples were collected in 2011, with the children's samples being collected about 3.5 years later (between 2014 and 2015). In the Norwegian mother-child cohort, the highest median concentrations in mothers were observed for TCEP (median = 72 ng/g), TBEP (median = 65 ng/g), TPP (median = 52 ng/g) and TDCPP (median = 30 ng/g) whereas, in our study, the highest median concentrations were observed for TCPP (median = 246 ng/g), TPP (median = 61 ng/g) and TEP (median = 49 ng/g). In both studies, only TPP was observed in high and similar concentrations. Among the children of the Norwegian cohort, the highest median concentrations were observed for TBEP (median = 318 ng/g), TPP (median = 63 ng/g), TCEP (median = 59 ng/g) and TDCPP (median = 31 ng/g). In our study, the highest median concentrations were observed for TCPP (median = 246.2 ng/g), TCDPP (median = 79.6 ng/g), TPP (median = 76.5 ng/g) and EHDPP (median = 73.5 ng/g). TDCPP and TPP were observed in high (though differing) concentrations in both studies. We do not have a clear explanation for these differences in countries from the same economic market and studied at roughly the same time; many factors may be involved, since these phosphorous compounds have many uses. Earlier European studies measuring OPFRs in other human matrices (such as urine and breastmilk) found that the highest median concentrations were also observed for TBEP, both in the children's urine (2 ng/mL) (Fromme et al., 2014) and in breastmilk (14.8 ng/g of lipid weight) (Beser et al., 2019).

OPFRs have been used in baby products containing polyurethane foam, such as nursing pillows and changing mats (Fang et al., 2013; Hoffman et al., 2015; Stapleton et al., 2011). A Californian study reported that the most common flame retardant detected in baby products was TDCPP (detection frequency 36 %), followed by components (including TPP) typically found in the "Firemaster 550" commercial mixture (detection frequency 17 %) (Stapleton et al., 2011). Higher TBEP exposure to among children (in comparison to mothers) can also be explained by the particular higher-frequency hand-to-mouth behaviour of children. This OPFR is specifically used in floor polishes (Van den Eede et al., 2013; Wei et al., 2015), though we did not find any correlation between TBEP concentrations in post-natal exposures and house dust concentrations.

In the present study, correlations between pre- and post-natal exposures to OPFRs were very weak, with the highest correlation being for TCPP ($r = 0.27$). This was also observed by Kucharska et al., (2015). This absence of correlations might be explained by changes to habits or lifestyle (resulting in different sources of exposure) between pregnancy and the child reaching 3.5 years of age, or by different pathways of exposure between adults and children.

As in our study, Kucharska et al., (2015) assessed correlations between post-natal exposures and OPFR concentrations in house dust for TBEP, EHDPP and TDCPP, and found a significant association for TBEP only. In our study, a higher number of correlations between hair and dust were assessed, and the only (and weak) significant association was observed for TEP ($r = -0.02$, p .value = 0.00). House dust ingestion has not appeared as the main contributor to children's exposure to OPFRs in this study, even for TBEP (sometimes referred as TBOEP) for which dust is often considered as an important pathway (Chupeau et al., 2020). One possible explanation is, as observed in Australia (He et al., 2018), food is a major pathway for several OPFRs.

With regard to potential determinants of pre-natal exposure to OPFRs in our present study, co-exposures to other flame retardants such as BDE₂₀₉ and BDE₄₇ were most consistently associated. These positive associations can be explained by common sources, the indoor persistence of BDE₂₀₉ and/or by concomitant exposure to consumer products produced before and after restrictions on PBDE use came into force, and their replacement by OPFRs (Van der Veen and de Boer, 2012). These positive associations can also be explained by a high number of electronic devices or by furniture in households. In the present study, BDE₂₀₉

could not be measured in children's hair samples. Post-natal exposure to BDE₄₇ was also associated with high post-natal exposure to 3 OPFRs (EHDPP, TBP, and TCPP).

Of the personal and socio-demographic factors, higher household income was consistently associated with lower pre- or post-natal exposure to several OPFRs (EHDPP, TEP, TMCP, TBP, TDCPP) and a similar tendency was observed with the highest level of maternal education being associated with lower OPFR exposure (EHDPP, TDCPP, TEP). This suggests that a higher socioeconomic status might be associated with lower OPFR exposure. Findings from other studies on the relationship between socioeconomic status and OPFR are both scarce and inconsistent. (Phillips et al., 2018) did not observe a significant relation between mother education and exposure of children to OPFR, while (Hammel et al., 2021) noticed an influence of socioeconomic status for some. In their review of all types of flame retardants (mainly PBDEs) (Arvaniti and Kalantzi, 2021) noticed higher exposure to flame retardants in lower-income households, influenced by quality of domestic furniture, inadequate ventilation, dietary habits (such as ingestion of highly contaminated food or malnutrition) are considered important determinants. Interestingly, pre-pregnancy BMI higher than 30 kg/m² was associated with an increase of pre-natal exposure for all studied OPFRs except TBEP, suggesting either possible physiological mechanisms or a specific lifestyle influence. (Hoffman et al., 2017) did not observe such an association for metabolites of TDCIPP and TPHP, and observations on organophosphorus insecticides reported conflicting results (Pinos et al., 2021). Breastfeeding appears not to be a major determinant of OPFR exposure observed at 3.5 years.

The present study suggests that few housing characteristics are capable of impacting OPFR exposure. Home renovation work in the past year has consistently been associated with higher OPFR exposure (TBP, TCEP, TCPP, TDCPP, TMCP and TPP), suggesting a potential release by old materials and/or new items of furniture. Such an association was observed by (Cequier et al., 2015) for one OPFR in air, though not by (Araki et al., 2014) for OPFRs in dust. The presence of parquet or lino in the child's bedroom was associated with higher post-natal exposure to TBEP, as in (Araki et al., 2014)'s study; this can be explained by the use of this particular OPFR as a floor varnish (Van der Veen and de Boer, 2012; Wei et al., 2015). We did not have information about the number of pillows in the home, and were therefore unable to assess any associations between these potential determinants and post-natal exposure to OPFRs (specifically, TDCPP and TPP) found in high concentrations in children and used in the manufacture of pillows.

5. Conclusion

This study is the first to provide representative populational assessment of exposure to OPFRs at nationwide level in France. Our results show that these children were exposed, both during pregnancy and in their early years, to a variety of OPFRs, with a high prevalence of exposure for some: for instance EHDPP, TDCPP and TPP exposures were above the limit of detection for >90 % of both pre-and post-natal exposures. In addition to exposure prevalence, recent neurotoxic studies have shown OPFRs to be neurotoxic via non-cholinergic pathways including disruption of both glutamate and gamma-aminobutyric acid (GABA) and of the endocrine system (Patisaul et al., 2021); a better understanding of the resulting health effects is called for. Because this study was not specifically designed to identify the main determinants and sources of OPFRs exposure, additional research on this issue is needed, to help with setting up public policy aimed at reducing OPFRs exposure.

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CRedit authorship contribution statement

Z. Chupeau: Methodology, Formal analysis, Data curation, Writing – original draft. **F. Mercier:** Methodology, Writing – review & editing, Supervision. **E. Rouxel:** Methodology, Formal analysis. **B. Le Bot:** Methodology, Writing – review & editing, Supervision, Funding acquisition, Project administration. **G. Chauvet:** Methodology, Writing – review & editing. **T. Siméon:** Data curation, Methodology, Writing – review & editing. **N. Bonvallot:** Methodology, Writing – review & editing. **C. Zaros:** Investigation, Writing – review & editing. **C. Chevrier:** Methodology, Writing – review & editing, Supervision. **P. Glorionec:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2022.107435>.

References

- Andresen, J.A., Grundmann, A., Bester, K., 2004. Organophosphorus flame retardants and plasticisers in surface waters. *Sci. Total Environ.* 332 (1-3), 155–166. <https://doi.org/10.1016/j.scitotenv.2004.04.021>.
- Appenzeller, B.M.R., Hardy, E.M., Grova, N., Chata, C., Fay's, F., Briand, O., Schroeder, H., Duca, R.-C., 2017. Hair analysis for the biomonitoring of pesticide exposure: comparison with blood and urine in a rat model. *Arch. Toxicol.* 91 (8), 2813–2825. <https://doi.org/10.1007/s00204-016-1910-9>.
- Araki, A., Saito, I., Kanazawa, A., Morimoto, K., Nakayama, K., Shibata, E., Tanaka, M., Takigawa, T., Yoshimura, T., Chikara, H., Saijo, Y., Kishi, R., 2014. Phosphorus flame retardants in indoor dust and their relation to asthma and allergies of inhabitants. *Indoor Air* 24 (1), 3–15. <https://doi.org/10.1111/ina.12054>.
- Arvaniti, O.S., Kalantzi, O.-I., 2021. Determinants of flame retardants in non-occupationally exposed individuals - A review. *Chemosphere* 263, 127923. <https://doi.org/10.1016/j.chemosphere.2020.127923>.

- European Flame Retardant Association, 2007. Frequently Asked Questions on Flame Retardants.
- Ballesteros-Gómez, A., Aragón, Á., Van den Eede, N., de Boer, J., Covaci, A., 2016. Impurities of Resorcinol Bis(diphenyl phosphate) in Plastics and Dust Collected on Electric/Electronic Material. *Environ. Sci. Technol.* 50 (4), 1934–1940. <https://doi.org/10.1021/acs.est.5b05351>.
- Béranger, R., Hardy, E.M., Dexet, C., Guldner, L., Zaros, C., Nougadère, A., Metten, M.-A., Chevrier, C., Appenzeller, B.M.R., 2018. Multiple pesticide analysis in hair samples of pregnant French women: Results from the ELFE national birth cohort. *Environ. Int.* 120, 43–53. <https://doi.org/10.1016/j.envint.2018.07.023>.
- Bergh, C., Torngrip, R., Emenius, G., Östman, C., 2011. Organophosphate and phthalate esters in air and settled dust - a multi-location indoor study: Organophosphate and phthalate esters in air and settled dust. *Indoor Air* 21, 67–76. <https://doi.org/10.1111/j.1600-0668.2010.00684.x>.
- Beser, M.I., Pardo, O., Beltrán, J., Yusà, V., 2019. Determination of 21 perfluoroalkyl substances and organophosphorus compounds in breast milk by liquid chromatography coupled to orbitrap high-resolution mass spectrometry. *Anal. Chim. Acta* 1049, 123–132. <https://doi.org/10.1016/j.aca.2018.10.033>.
- Björnsdóttir, M.K., Romera-García, E., Borrull, J., de Boer, J., Rubio, S., Ballesteros-Gómez, A., 2018. Presence of diphenyl phosphate and aryl-phosphate flame retardants in indoor dust from different microenvironments in Spain and the Netherlands and estimation of human exposure. *Environ. Int.* 112, 59–67. <https://doi.org/10.1016/j.envint.2017.11.028>.
- Blanchard, O., Mercier, F., Ramalho, O., Mandin, C., Le Bot, B., Glorennec, P., 2014. Measurements of semi-volatile organic compounds in settled dust: influence of storage temperature and duration. *Indoor Air* 24 (2), 125–135. <https://doi.org/10.1111/ina.12066>.
- Blondel, B., Kermarrec, M., 2011. les naissances en 2010 et leur évolution depuis 2003 132.
- Blum, A., Behl, M., Birnbaum, L.S., Diamond, M.L., Phillips, A., Singla, V., Sipes, N.S., Stapleton, H.M., Venier, M., 2019. Organophosphate Ester Flame Retardants: Are They a Regrettable Substitution for Polybrominated Diphenyl Ethers? *Environ. Sci. Technol. Lett.* 6 (11), 638–649. <https://doi.org/10.1021/acs.estlett.9b00582>.
- Brommer, S., Harrad, S., den Eede, N.V., Covaci, A., 2012. Concentrations of organophosphate esters and brominated flame retardants in German indoor dust samples. *J. Environ. Monit.* 14, 2482–2487. <https://doi.org/10.1039/C2EM303030E>.
- Canbaz, D., van Velzen, M.J.M., Hallner, E., Zwinderman, A.H., Wickman, M., Leonards, P.E.G., van Ree, R., van Rijt, L.S., 2016. Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma. *Indoor Air* 26 (3), 403–413. <https://doi.org/10.1111/ina.12221>.
- Carignan, C.C., Mínguez-Alarcón, L., Williams, P.L., Meeker, J.D., Stapleton, H.M., Butt, C.M., Toth, T.L., Ford, J.B., Hauser, R., 2018. Paternal urinary concentrations of organophosphate flame retardant metabolites, fertility measures, and pregnancy outcomes among couples undergoing in vitro fertilization. *Environ. Int.* 111, 232–238. <https://doi.org/10.1016/j.envint.2017.12.005>.
- Castorina, R., Butt, C., Stapleton, H.M., Avery, D., Harley, K.G., Holland, N., Eskenazi, B., Bradman, A., 2017. Flame retardants and their metabolites in the homes and urine of pregnant women residing in California (the CHAMACOS cohort). *Chemosphere* 179, 159–166. <https://doi.org/10.1016/j.chemosphere.2017.03.076>.
- Cequier, E., Ionas, A.C., Covaci, A., Marcé, R.M., Becher, G., Thomsen, C., 2014a. Occurrence of a Broad Range of Legacy and Emerging Flame Retardants in Indoor Environments in Norway. *Environ. Sci. Technol.* 48 (12), 6827–6835. <https://doi.org/10.1021/es500516u>.
- Cequier, E., Marcé, R.M., Becher, G., Thomsen, C., 2014b. A high-throughput method for determination of metabolites of organophosphate flame retardants in urine by ultra performance liquid chromatography–high resolution mass spectrometry. *Anal. Chim. Acta* 845, 98–104. <https://doi.org/10.1016/j.aca.2014.06.026>.
- Cequier, E., Sakhi, A.K., Marcé, R.M., Becher, G., Thomsen, C., 2015. Human exposure pathways to organophosphate triesters — A biomonitoring study of mother–child pairs. *Environ. Int.* 75, 159–165. <https://doi.org/10.1016/j.envint.2014.11.009>.
- Charles, M.A., Thierry, X., Lanoe, J.-L., Bois, C., Dufourg, M.-N., Popa, R., Cheminat, M., Zaros, C., Geay, B., 2020. Cohort Profile: The French national cohort of children (ELFE): birth to 5 years. *Int. J. Epidemiol.* 49, 368–369. <https://doi.org/10.1093/ije/dy227>.
- Chupeau, Z., Bonvallot, N., Mercier, F., Le Bot, B., Chevrier, C., Glorennec, P., 2020. Organophosphorus Flame Retardants: A Global Review of Indoor Contamination and Human Exposure in Europe and Epidemiological Evidence. *Int. J. Environ. Res. Public Health* 17, 6713. <https://doi.org/10.3390/ijerph17186713>.
- Coelho, S.D., Sousa, A.C.A., Isobe, T., Kim, J.-W., Kunisue, T., Nogueira, A.J.A., Tanabe, S., 2016. Brominated, chlorinated and phosphate organic contaminants in house dust from Portugal. *Sci. Total Environ.* 569–570, 442–449. <https://doi.org/10.1016/j.scitotenv.2016.06.137>.
- Deville, J.-C., Särndal, C.-E., Sautory, O., 1993. Generalized Raking Procedures in Survey Sampling. *J. Am. Stat. Assoc.* 88 (423), 1013–1020. <https://doi.org/10.1080/01621459.1993.10476369>.
- Deziel, N.C., Yi, H., Stapleton, H.M., Huang, H., Zhao, N., Zhang, Y., 2018. A case-control study of exposure to organophosphate flame retardants and risk of thyroid cancer in women. *BMC Cancer* 18, 637. <https://doi.org/10.1186/s12885-018-4553-9>.
- Doherty, B.T., Hammel, S.C., Daniels, J.L., Stapleton, H.M., Hoffman, K., 2019. Organophosphate Esters: Are These Flame Retardants and Plasticizers Affecting Children's Health? *Curr. Environ. Health Rpt* 6 (4), 201–213. <https://doi.org/10.1007/s40572-019-00258-0>.
- Esteban, M., Castaño, A., 2009. Non-invasive matrices in human biomonitoring: A review. *Environ. Int.* 35 (2), 438–449. <https://doi.org/10.1016/j.envint.2008.09.003>.
- Fang, M., Webster, T.F., Gooden, D., Cooper, E.M., McClean, M.D., Carignan, C., Makey, C., Stapleton, H.M., 2013. Investigating A Novel Flame Retardant Known as V6: Measurements in Baby Products, House Dust and Car Dust. *Environ. Sci. Technol.* 47 (9), 4449–4454. <https://doi.org/10.1021/es400032v>.
- Fromme, H., Lahrz, T., Kraft, M., Fembacher, L., Mach, C., Dietrich, S., Burkardt, R., Völkel, W., Göen, T., 2014. Organophosphate flame retardants and plasticizers in the air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3). *Environ. Int.* 71, 158–163. <https://doi.org/10.1016/j.envint.2014.06.016>.
- Hajeb, P., Castaño, A., Cequier, E., Covaci, A., López, M.E., Antuña, A.G., Haug, L.S., Henríquez-Hernández, L.A., Melymuk, L., Pérez Luzardo, O., Thomsen, C., Vorkamp, K., 2022. Critical review of analytical methods for the determination of flame retardants in human matrices. *Anal. Chim. Acta* 1193, 338828. <https://doi.org/10.1016/j.aca.2021.338828>.
- Hammel, S.C., Stapleton, H.M., Eichner, B., Hoffman, K., 2021. Reconsidering an Appropriate Urinary Biomarker for Flame Retardant Tris(1-chloro-2-propyl) Phosphate (TCIPP) Exposure in Children. *Environ. Sci. Technol. Lett.* 8, 80–85. <https://doi.org/10.1021/acs.estlett.0c00794>.
- Harrad, S., Brommer, S., Mueller, J.F., 2016. Concentrations of organophosphate flame retardants in dust from cars, homes, and offices: An international comparison. *Emerging Contaminants, Special Issue: A Tribute to Hidetaka Takigami 2*, 66–72. <https://doi.org/10.1016/j.emcon.2016.05.002>.
- Hartmann, P.C., Bürgi, D., Giger, W., 2004. Organophosphate flame retardants and plasticizers in indoor air. *Chemosphere* 57, 781–787. <https://doi.org/10.1016/j.chemosphere.2004.08.051>.
- He, C., Wang, X., Tang, S., Thai, P., Li, Z., Baduel, C., Mueller, J.F., 2018. Concentrations of Organophosphate Esters and Their Specific Metabolites in Food in Southeast Queensland, Australia: Is Dietary Exposure an Important Pathway of Organophosphate Esters and Their Metabolites? *Environ. Sci. Technol.* 52, 12765–12773. <https://doi.org/10.1021/acs.est.8b03043>.
- Helsel, D.R., 2011. Statistics for Censored Environmental Data Using Minitab and R. John Wiley & Sons.
- Hoffman, K., Garantziotis, S., Birnbaum, L.S., Stapleton, H.M., 2015. Monitoring Indoor Exposure to Organophosphate Flame Retardants: Hand Wipes and House Dust. *Environ. Health Perspect.* 123, 160–165. <https://doi.org/10.1289/ehp.1408669>.
- Hoffman, K., Lorenzo, A., Butt, C.M., Adair, L., Herring, A.H., Stapleton, H.M., Daniels, J. L., 2017. Predictors of urinary flame retardant concentration among pregnant women. *Environ. Int.* 98, 96–101. <https://doi.org/10.1016/j.envint.2016.10.007>.
- Jin, Y., Hein, M.J., Deddens, J.A., Hines, C.J., 2011. Analysis of Lognormally Distributed Exposure Data with Repeated Measures and Values below the Limit of Detection Using SAS: The Annals of Occupational Hygiene 55, 97–112. <https://doi.org/10.1093/annhyg/meq061>.
- Kemmlen, S., Hahn, O., Jann, O., 2003. Emissions of organophosphate and brominated flame retardants from selected consumer products and building materials. *Atmos. Environ.* 37, 5485–5493. <https://doi.org/10.1016/j.atmosenv.2003.09.025>.
- Kucharska, A., Cequier, E., Thomsen, C., Becher, G., Covaci, A., Voorspoels, S., 2015a. Assessment of human hair as an indicator of exposure to organophosphate flame retardants. Case study on a Norwegian mother-child cohort. *Environ. Int.* 83, 50–57. <https://doi.org/10.1016/j.envint.2015.05.015>.
- Kucharska, A., Covaci, A., Vanermen, G., Voorspoels, S., 2015b. Non-invasive biomonitoring for PFRs and PBDEs: new insights in analysis of human hair externally exposed to selected flame retardants. *Sci. Total Environ.* 505, 1062–1071. <https://doi.org/10.1016/j.scitotenv.2014.10.043>.
- Langer, S., Fredricsson, M., Weschler, C.J., Bekö, G., Strandberg, B., Remberger, M., Toftum, J., Clausen, G., 2016. Organophosphate esters in dust samples collected from Danish homes and daycare centers. *Chemosphere* 154, 559–566. <https://doi.org/10.1016/j.chemosphere.2016.04.016>.
- Larsson, K., de Wit, C.A., Sellström, U., Sahlström, L., Lindh, C.H., Berglund, M., 2018. Brominated Flame Retardants and Organophosphate Esters in Preschool Dust and Children's Hand Wipes. *Environ. Sci. Technol.* 52, 4878–4888. <https://doi.org/10.1021/acs.est.8b00184>.
- Martinez, G., Niu, J., Takser, L., Bellenger, J.-P., Zhu, J., 2021. A review on the analytical procedures of halogenated flame retardants by gas chromatography coupled with single quadrupole mass spectrometry and their levels in human samples. *Environ. Pollut.* 285, 117476. <https://doi.org/10.1016/j.envpol.2021.117476>.
- Meeker, J.D., Cooper, E.M., Stapleton, H.M., Hauser, R., 2013. Urinary Metabolites of Organophosphate Flame Retardants: Temporal Variability and Correlations with House Dust Concentrations. *Environ. Health Perspect.* 121, 580–585. <https://doi.org/10.1289/ehp.1205907>.
- Mercier, F., Gilles, E., Saramito, G., Glorennec, P., Le Bot, B., 2014. A multi-residue method for the simultaneous analysis in indoor dust of several classes of semi-volatile organic compounds by pressurized liquid extraction and gas chromatography/tandem mass spectrometry. *J. Chromatogr. A* 1336, 101–111. <https://doi.org/10.1016/j.chroma.2014.02.004>.
- Niang, B., Glorennec, P., Bot, B.L., Mercier, F., Chevrier, C., Bonvallot, N., 2019. Hiérarchisation de contaminants anthropiques semi-volatils pour l'étude des risques. Le cas des retardateurs de flamme organophosphorés. *Environnement, Risques & Santé* 18, 222–234. <https://doi.org/10.1684/ers.2019.1309>.
- Pantelaki, I., Voutsas, D., 2021. Organophosphate esters in inland and coastal waters in northern Greece. *Sci. Total Environ.* 800, 149544. <https://doi.org/10.1016/j.scitotenv.2021.149544>.
- Patisaul, H.B., Behl, M., Birnbaum, L.S., Blum, A., Diamond, M.L., Rojello, F.S., Hogberg, H.T., Kwiatkowski, C.F., Page, J.D., Soehl, A., Stapleton, H.M., 2021. Beyond Cholinesterase Inhibition: Developmental Neurotoxicity of Organophosphate Ester Flame Retardants and Plasticizers. *Environ. Health Perspect.* 129, 105001. <https://doi.org/10.1289/EHP9285>.

- Peng, F.-J., Emond, C., Hardy, E.M., Sauvageot, N., Alkerwi, A., Lair, M.-L., Appenzeller, B.M.R., 2021. Population-based biomonitoring of exposure to persistent and non-persistent organic pollutants in the Grand Duchy of Luxembourg: Results from hair analysis. *Environ. Int.* 153, 106526 <https://doi.org/10.1016/j.envint.2021.106526>.
- Percy, Z., La Guardia, M.J., Xu, Y., Hale, R.C., Dietrich, K.N., Lanphear, B.P., Yoltos, K., Vuong, A.M., Cecil, K.M., Braun, J.M., Xie, C., Chen, A., 2020. Concentrations and loadings of organophosphate and replacement brominated flame retardants in house dust from the home study during the PBDE phase-out. *Chemosphere* 239, 124701. <https://doi.org/10.1016/j.chemosphere.2019.124701>.
- Persson, J., Wang, T., Hagberg, J., 2018. Organophosphate flame retardants and plasticizers in indoor dust, air and window wipes in newly built low-energy preschools. *Sci. Total Environ.* 628–629, 159–168. <https://doi.org/10.1016/j.scitotenv.2018.02.053>.
- Phillips, A.L., Hammel, S.C., Hoffman, K., Lorenzo, A.M., Chen, A., Webster, T.F., Stapleton, H.M., 2018. Children's residential exposure to organophosphate ester flame retardants and plasticizers: Investigating exposure pathways in the TESIE study. *Environ. Int.* 116, 176–185. <https://doi.org/10.1016/j.envint.2018.04.013>.
- Pinos, H., Carrillo, B., Merchán, A., Biosca-Brull, J., Pérez-Fernández, C., Colomina, M.T., Sánchez-Santed, F., Martín-Sánchez, F., Collado, P., Arias, J.L., Conejo, N.M., 2021. Relationship between Prenatal or Postnatal Exposure to Pesticides and Obesity: A Systematic Review. *Int. J. Environ. Res. Public Health* 18, 7170. <https://doi.org/10.3390/ijerph18137170>.
- Poon, S., Koren, G., Carnevale, A., Aleksa, K., Ling, J., Ozsarfaty, J., Kapur, B.M., Bagli, D., 2018. Association of In Utero Exposure to Polybrominated Diphenyl Ethers With the Risk of Hypospadias. *JAMA Pediatr* 172, 851–856. <https://doi.org/10.1001/jamapediatrics.2018.1492>.
- Reemtsma, T., Lingott, J., Roegler, S., 2011. Determination of 14 monoalkyl phosphates, dialkyl phosphates and dialkyl thiophosphates by LC-MS/MS in human urinary samples. *Sci. Total Environ.* 409, 1990–1993. <https://doi.org/10.1016/j.scitotenv.2011.01.032>.
- Schindler, B.K., Förster, K., Angerer, J., 2009. Determination of human urinary organophosphate flame retardant metabolites by solid-phase extraction and gas chromatography–tandem mass spectrometry. *J. Chromatogr. B* 877, 375–381. <https://doi.org/10.1016/j.jchromb.2008.12.030>.
- Sha, B., Dahlberg, A.-K., Wiberg, K., Ahrens, L., 2018. Fluorotelomer alcohols (FTOHs), brominated flame retardants (BFRs), organophosphorus flame retardants (OPFRs) and cyclic volatile methylsiloxanes (cVMSs) in indoor air from occupational and home environments. *Environ. Pollut.* 241, 319–330. <https://doi.org/10.1016/j.envpol.2018.04.032>.
- Sheldon, L.S., Hites, R.A., 1978. Organic compounds in the Delaware River. *Environ. Sci. Technol.* 12, 1188–1194. <https://doi.org/10.1021/es60146a006>.
- Soubry, A., Hoyo, C., Butt, C.M., Fieuws, S., Price, T.M., Murphy, S.K., Stapleton, H.M., 2017. Human exposure to flame-retardants is associated with aberrant DNA methylation at imprinted genes in sperm. *Environmental. Epigenetics* 3, dvx003. <https://doi.org/10.1093/eep/dvx003>.
- Staaf, T., Östman, C., 2005. Organophosphate triesters in indoor environments. *J. Environ. Monit.* 7, 883–887. <https://doi.org/10.1039/B506631J>.
- Stapleton, H.M., Klosterhaus, S., Eagle, S., Fuh, J., Meeker, J.D., Blum, A., Webster, T.F., 2009. Detection of Organophosphate Flame Retardants in Furniture Foam and U.S. House Dust. *Environ. Sci. Technol.* 43, 7490–7495. <https://doi.org/10.1021/es9014019>.
- Stapleton, H.M., Klosterhaus, S., Keller, A., Ferguson, P.L., van Bergen, S., Cooper, E., Webster, T.F., Blum, A., 2011. Identification of Flame Retardants in Polyurethane Foam Collected from Baby Products. *Environ. Sci. Technol.* 45, 5323–5331. <https://doi.org/10.1021/es2007462>.
- Stapleton, H.M., Sharma, S., Getzinger, G., Ferguson, P.L., Gabriel, M., Webster, T.F., Blum, A., 2012. Novel and high volume use flame retardants in US couches reflective of the 2005 PentaBDE phase out. *Environ. Sci. Technol.* 46, 13432–13439. <https://doi.org/10.1021/es303471d>.
- Sugeng, E.J., Leonards, P.E.G., van de Bor, M., 2017. Brominated and organophosphorus flame retardants in body wipes and house dust, and an estimation of house dust hand-loadings in Dutch toddlers. *Environ. Res.* 158, 789–797. <https://doi.org/10.1016/j.envres.2017.07.035>.
- Sundkvist, A.M., Olofsson, U., Haglund, P., 2010. Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. *J. Environ. Monit.* 12, 943–951. <https://doi.org/10.1039/b921910b>.
- Tang, B., Xiong, S.-M., Zheng, J., Wang, M.-H., Cai, F.-S., Luo, W.-K., Xu, R.-F., Yu, Y.-J., 2021. Analysis of polybrominated diphenyl ethers, hexabromocyclododecanes, and legacy and emerging phosphorus flame retardants in human hair. *Chemosphere* 262, 127807. <https://doi.org/10.1016/j.chemosphere.2020.127807>.
- Van den Eede, N., Neels, H., Jorens, P.G., Covaci, A., 2013. Analysis of organophosphate flame retardant diester metabolites in human urine by liquid chromatography electrospray ionisation tandem mass spectrometry. *J. Chromatogr. A* 1303, 48–53. <https://doi.org/10.1016/j.chroma.2013.06.042>.
- Van der Veen, I., de Boer, J., 2012. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere* 88, 1119–1153. <https://doi.org/10.1016/j.chemosphere.2012.03.067>.
- Völkel, W., Fuchs, V., Wöckner, M., Fromme, H., 2018. Toxicokinetic of tris(2-butoxyethyl) phosphate (TBOEP) in humans following single oral administration. *Arch. Toxicol.* 92, 651–660. <https://doi.org/10.1007/s00204-017-2078-7>.
- Vykoukalová, M., Venier, M., Vojta, Š., Melymuk, L., Bečanová, J., Romanak, K., Prokeš, R., Okeme, J.O., Saini, A., Diamond, M.L., Klánová, J., 2017. Organophosphate esters flame retardants in the indoor environment. *Environ. Int.* 106, 97–104. <https://doi.org/10.1016/j.envint.2017.05.020>.
- Wei, G.-L., Li, D.-Q., Zhuo, M.-N., Liao, Y.-S., Xie, Z.-Y., Guo, T.-L., Li, J.-J., Zhang, S.-Y., Liang, Z.-Q., 2015. Organophosphorus flame retardants and plasticizers: Sources, occurrence, toxicity and human exposure. *Environ. Pollut.* 196, 29–46. <https://doi.org/10.1016/j.envpol.2014.09.012>.
- Wong, F., de Wit, C.A., Newton, S.R., 2018. Concentrations and variability of organophosphate esters, halogenated flame retardants, and polybrominated diphenyl ethers in indoor and outdoor air in Stockholm, Sweden. *Environ. Pollut.* 240, 514–522. <https://doi.org/10.1016/j.envpol.2018.04.086>.
- www.flameretardants-online.com, 2022. The flame retardants market | FLAMERETARDANTS-ONLINE [WWW Document]. www.flameretardants-online.com. URL <https://www.flameretardants-online.com/flame-retardants/market> (accessed 6.7.22).
- Yang, Y., Chen, P., Ma, S., Lu, S., Yu, Y., An, T., 2022. A critical review of human internal exposure and the health risks of organophosphate ester flame retardants and their metabolites. *Crit. Rev. Environ. Sci. Technol.* 52, 1528–1560. <https://doi.org/10.1080/10643389.2020.1859307>.
- Yon, T., Saramito, G., Lecorgne, A., Goyat, Q., Glorennec, P., Le Bot, B., Mercier, F., 2022. Simultaneous determination of organophosphorus and brominated flame retardants and polychlorinated biphenyls in hair by pressurized liquid extraction and gas chromatography/tandem mass spectrometry. 10.26434/chemrxiv-2022-ng6d8.
- Zhao, X., Liu, L., Pang, J., 2021. Hair as a noninvasive biomarker of human exposure to the endocrine disruptors polybrominated diphenyl ethers: a meta-analysis. *Environ. Monit. Assess.* 193, 371. <https://doi.org/10.1007/s10661-021-09155-2>.
- Zheng, X., Sun, R., Qiao, L., Guo, H., Zheng, J., Mai, B., 2017. Flame retardants on the surface of phones and personal computers. *Sci. Total Environ.* 609, 541–545. <https://doi.org/10.1016/j.scitotenv.2017.07.202>.
- Zhou, L., Hiltcher, M., Püttmann, W., 2017. Occurrence and human exposure assessment of organophosphate flame retardants in indoor dust from various microenvironments of the Rhine/Main region, Germany. *Indoor Air* 27, 1113–1127. <https://doi.org/10.1111/ina.12397>.

CHAPITRE 3 : Exposition pré- et post-natale aux RFOP et neurodéveloppement, en France.

3. Exposition pré- et post- natale aux RFOP et neurodéveloppement, en France

À noter : l'article présenté dans cette partie est en cours d'écriture. Il n'a pas encore été relu par les co-auteurs et les révisions linguistiques n'ont pas encore été réalisées.

Après avoir estimé l'exposition aux RFOP des enfants avant leur naissance et au cours de leurs premières années de vie, ainsi que les déterminants possibles de ces expositions, nous avons étudié, dans cette dernière partie de thèse, les effets de ces expositions sur le neurodéveloppement de l'enfant à 3.5 ans. 388 paires mères-enfants de la cohorte Elfe ont été incluses dans ces analyses. Les expositions pré- et post-natales ont été estimées grâce aux concentrations de 9 RFOP mesurées dans les cheveux des mamans et des enfants collectés, respectivement, à la naissance et à 3,5 ans. Le développement cognitif de l'enfant a été évalué avec le module « Picture Similarities » issu de la seconde édition l'échelle BAS. Le BAS est un test reconnu et validé sur le plan international qui a déjà été utilisé dans la Millenium Cohort Study à 3 et 5 ans (George et al., 2007). Le module « Picture Similarities » fait appel chez l'enfant aux capacités : de résolution non-verbale de problèmes (raisonnement inductif), de perception et d'analyse visuelle, d'attribution d'une signification à une image, de développement et de test d'hypothèse et de recours à la médiation verbale. Un faible score peut également refléter une impulsivité (répondre sans vérifier sa réponse). Ce module a été choisi par Elfe, car il répond à un ensemble de critères pratiques. Le premier critère est que le test peut être administré par un enquêteur n'ayant pas de formation médicale et n'ayant pas l'habitude de travailler avec les jeunes enfants. Le second critère est que les règles du jeu sont simples afin que l'enquêteur ait peu d'explication à donner à l'enfant. Le troisième critère est que la cotation des réponses de l'enfant est automatique et non ambiguë pour en rendre aisée l'appropriation par l'enquêteur. Le quatrième critère est que les règles d'arrêt du jeu sont complètement automatisées pour en éviter la gestion à l'enquêteur. Le dernier critère est que le jeu est court, afin de tenir compte des capacités attentionnelles de l'enfant et de respecter la disponibilité des parents en limitant le temps de présence au domicile. La passation est

réalisée à l'aide d'un jeu de 33 cartes et de 33 planches successives de 4 images. On présente à l'enfant successivement chaque planche de 4 images, avec la carte associée qui représente une 5^{ème} image. L'enfant doit indiquer avec quelle image de la planche sa carte doit être associée (« laquelle va le mieux ») par exemple en plaçant sa carte sous l'une des 4 images de la planche.

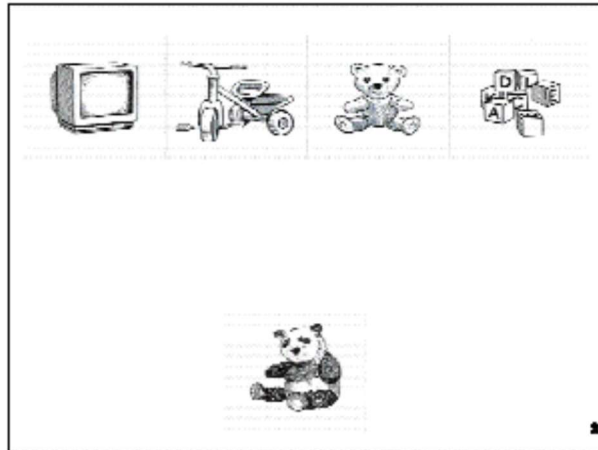


Figure 6. Image d'illustration du test « Picture Similarities ».

Les 5 premières planches sont des planches de formation au jeu. Le test s'arrête dès que l'enfant a fait 6 erreurs sur 8 planches consécutives. Le score brut (raw score) est calculé en additionnant le nombre de bonnes réponses (1 point par bonne réponse). Dans la version originale du test, le nombre maximal de planches présenté à l'enfant est fonction de l'âge : 23, 28 ou 33 planches si l'enfant avait respectivement entre 2 ans 6 mois et 3 ans 5 mois, 3 ans 6 mois et 4 ans 5 mois, 4 ans 6 mois et 7 ans 11 mois. Cependant, dans Elfe, cette règle d'arrêt n'a pas été respectée et il est possible que 33 planches aient été présentées à des enfants s'ils n'avaient pas eu 6 erreurs sur 8 planches consécutives. Nous avons donc décidé d'ajuster tous les modèles sur l'âge (en mois) de l'enfant à la passation du test, car la règle d'arrêt originale du test n'ayant pas été respectée dans Elfe, le calcul du score ne tient donc pas compte de l'âge de l'enfant. D'ailleurs, les enfants plus âgés avaient de meilleurs scores. Un tableau de correspondance permettait d'obtenir le score de capacité (ability score) en fonction du score brut (raw score) et du nombre maximal de planches théoriques de planches présenté

à l'enfant ("Etude longitudinale française depuis l'enfance"). C'est le score de capacité que nous avons utilisé dans nos modèles de régression. L'augmentation de l'exposition prénatale à 8 RFOP parmi les 9 était associée à une diminution du score du test « Picture Similarities » avec des associations significatives pour 2 RFOP. L'augmentation de l'exposition postnatale à 7 RFOP parmi les 9 étudiés était associée à une diminution du score du test « Picture Similarities » avec des associations statistiquement significatives pour 5 RFOP.

Toutes les analyses ont été pondérées afin d'extrapoler les résultats à l'ensemble des naissances françaises en 2011. Nous avons utilisé des modèles mono-polluant pour évaluer l'association entre l'exposition des enfants entre chaque RFOP et la cognition. Nous avons utilisé un Graphique Acyclique Dirigé pour sélectionner les variables d'ajustement. Nous avons trouvé une diminution de 1,3 point du test PST par doublement de l'exposition prénatale au triethyl phosphate (TEP) et une diminution de 4,6 points pour le quatrième quartile par rapport au premier quartile des expositions au TNBP (valeurs $p < 0,05$). Plus inattendu, nous avons observé une augmentation de 6,2 points du score du PST pour une augmentation de l'exposition prénatale au TPHP. Concernant l'exposition postnatale, nous avons observé une diminution de 1,2 points pour l'EHDPP, 6 points pour le TBEP, 4,5 points pour le TCEP, 1,1 point pour le TDCPP et 8,7 points pour le TPHP, ajustée sur l'exposition prénatale. Il s'agit de la première étude française qui a évalué l'effet des RFOP sur le neurodéveloppement.

Early-life exposure to organophosphate flame retardants and child neurodevelopment, in a French national birth cohort.

Chupeau Z.¹, Siméon, T.³, Mercier F.¹, Le Bot B.¹, Chauvet G.², Bonvallot N.¹, Zaros C.³, Charles.M-A³, Glorennec P.¹, Chevrier C.¹

1. Univ Rennes, EHESP, Inserm, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, France.

2. Ensai (Irmair), Campus de Ker Lann, Bruz - France.

3. UM Ined-Inserm-EFS, France.

Abstract

The use of OPFR has increased dramatically in recent years, especially since the banning of PBDE in the early 2000s. Toxicological and epidemiological studies investigated potential adverse effect of prenatal exposure on neurodevelopment but they obtained varying results and only one study assessed postnatal exposure on child neurodevelopment. We aimed to explore association between pre- and post-natal exposure to OPFR and non verbal cognitive abilities at 3.5 years using hair concentrations as an exposure metric. We included 388 mother-child pairs from the French Elfe nationwide cohort. Pre- and post-natal exposures were estimated with concentrations of 9 OPFR measured in the hair of mothers collected at birth and children at 3.5 years, respectively. The child's cognitive development was evaluated using the Picture similarities test (PST) from the British ability scale (BAS) at 3.5 years. All analyses were weighted in order to transpose them to French birth in 2011. We used mono-pollutant model to assess association between children OPFR exposure and cognition. We used a Directed Acyclic Graph to select the adjustment variables. We found a 1.3 point decrease of PST test per twofold increase in prenatal exposure to triethyl phosphate (TEP) and a decrease of 4.6 points for the fourth quartile compared to the first quartile of tri-n-butyl phosphate (TBP) exposures (p.values <0.05). Unexpectidely, we observed an increase of 6.2 points on score of Picture Similarities test for an increase of triphenyl phosphate (TPP) prenatal exposure.

Concerning postnatal exposure, we observed a decrease of 1.2 points for ethylhexyl diphenyl phosphate (EHDPP), 6 points for tris(2-butoxyethyl) phosphate (TBEP), 4.5 points for tris(2-chloroethyl) phosphate (TCEP), 1.1 point for tris(1,3-dichloro-2-propyl) phosphate (TDCPP) and 8.7 points for triphenyl phosphate (TPP), adjusted on prenatal exposure. This is the first study conducted in France, which evaluated OPFR effect on neurodevelopment. As effects on non-verbal development cannot be ruled out from our observations, more studies are urgently required before drawing robust conclusion on the neurodevelopmental risks of these compounds.

Keywords: cognition, child, environmental health, chemical safety

Introduction

Organophosphorus flame retardants (OPFR) are chemical compounds that are added to many consumer products during the manufacturing process (Kemmler et al., 2003; van der Veen and de Boer, 2012). They are widely used in cars, electronics, furniture (Stapleton et al., 2009), nail polishes, and textiles (van der Veen and de Boer, 2012).

Since the 2000s, they have increasingly been used to replace polybrominated diphenyl ethers (PBDE), a family of brominated flame-retardants classified under the Stockholm Convention as persistent organic pollutants (POPs), and gradually banned (Blum et al., 2019; Chupeau et al., 2020; Stapleton et al., 2012). The worldwide consumption of flame-retardants amounts to more than 2.39 Million tons in 2019, including 18% of organophosphorus (www.flameretardants-online.com, 2022).

OPFR are not chemically bound in products and may be released into the environment via volatilization, leaching and/or abrasion. Thus, they can be found in biota, sediment, soil and water (Pantelaki and Voutsas, 2021), as well as in indoor environments ; they are also largely detected in humans especially in vulnerable population including pregnant women and children (Chupeau et al., 2020; van der Veen and de Boer, 2012; Wei et al., 2015). OPFR were also

measured and detected in human placenta (Ding et al., 2016) , and in breast milk (Beser et al., 2019; Sundkvist et al., 2010).

Studies on rodents found OPFR to be neurotoxic via no cholinergic pathways including perturbation of glutamate and gamma-aminobutyric acid (GABA) and disruption of the endocrine system or perturbation of others neurotransmitters (Patisaul et al., 2021). From zebrafish experiments, prenatal exposure to Tris(2-butoxyethyl)phosphate (TBEP) resulted in a decrease in gene expression of growth hormone-insulin-like growth factor (GH/IGF) (Liu et al., 2017) , the exposure to several OPFR appeared to alter the concurrent levels of thyroxine hormone (T4) (Liu et al., 2019; Wang et al., 2013) and oxidative stress and reduction of transcription of key genes involved in neurodevelopment were observed in juvenile zebrafish exposed to triphenyl phosphate (TPP), 2-ethylhexyl diphenyl phosphate (EHDPP) and TCEP (Gu et al., 2018). Another toxicological study orally exposed pregnant wistar rats dams to OPFR (triphenyl phosphate and a mixture of isopropylated triarylphosphate isomers) or a serotonin (5-HT) agonist 5-methoxytryptamine for 14 days. Relative abundance of genes responsible for the transport and synthesis of placental 5-HT were disrupted, and multiple neuroactive metabolites in the 5-HT and kynurenine metabolic pathways were upregulated. This study suggest that OPFR have the potential to affect the 5-HTergic system in the foetal forebrain by disrupting placental tryptophan metabolism (Rock et al., 2020).

Because children may be exposed to OPFR during a critical period of development such as during pregnancy or during their first years, the question of a possible role of OPFR on children neurodevelopmental health needs thus to be addressed. Previous epidemiological studies investigated the relation between pre- and post-natal exposure to OPFR and neurodevelopment of their children with varying results (Zhao et al., 2022). Several of them suggested an adverse impact of the prenatal exposure to OPFR on children's cognition including the language ability and fine motor skills between 2 and 3 years old (Doherty et al., 2019), intelligence at 7 years old (Castorina et al., 2017) and a global developmental scale which evaluated children's cognition, language and social development at two years (Liu et al.,

2021). Another study did not confirm this association with intelligence among 8-year-old children (Percy et al., 2021). The same study analyzed further the association between OPFR exposure during early childhood and cognition of 8-year-old children and reported adverse association specifically among children with more disadvantaged backgrounds for perceptual reasoning, verbal comprehension and working memory (Percy et al., 2022). Four studies focused on childhood behavior with OPFR exposure (Zhao et al., 2022). One of them observed a positive correlation between Σ OPFR exposure and externalizing problems but a negative correlation between Σ OPFR exposure and responsibility in children (Lipscomb et al., 2017). (Choi et al., 2021) found that maternal DPHP exposure increased the risk of ADHD in children (Zhao et al., 2022). (Doherty et al., 2019) suggested that prenatal BDCIPP exposure was positively associated with more adverse behaviors in offspring, including withdrawal and attention problems; conversely, ip-PPP exposure was associated with fewer behavioral symptoms, particularly internalizing behaviors. (Crawford et al., 2020) observed an association between prenatal exposure to BDCIPP and an increased risk of food responsiveness of children. Only one study assessed association between prenatal OPFR exposure and childhood emotional disorders (Doherty et al., 2019). It observed a negative association between prenatal exposure to ip-PPP and the risk of anxiety.

About half of these studies assessed exposure through urinary concentrations of OPFR metabolites measured for example in one or several maternal samples collected during pregnancy. Because of the relatively short biological half-lives of organophosphate flame retardants, the urinary concentrations of OPFR metabolites reflect short-term exposure, e.g. of the past few days or hours. Temporal variability studies of urinary concentrations indicated low to moderate reproducibility when using urinary spots for exposure assessment for most OPFR (Bastiaensen et al., 2021; Hoffman et al., 2014). Human hair is a non-invasive matrix with numerous advantages of simple and cost-effective sampling, transport and storage, sample stability, and properties of storage in its internal structure of chemicals present in the blood stream. While there is still no evidence that hair-measurements of OPFR reflect the internal dose, these measurements appear an appropriate predictor of cumulative exposure to OPFR

present in the individual environments, since these compounds are not bounded to particular matters (Hajeb et al., 2022; Kucharska et al., 2015; Yang et al., 2022).

In the French Elfe birth cohort, we aim at exploring the association between prenatal exposure to multiple OPFR and neurodevelopmental outcome at 3.5 years taking into account postnatal exposure to OPFR, using hair-concentration measurements.

Material and methods

Population

ELFE (*“Etude longitudinale française depuis l'enfance”*) is a French national birth cohort. Its objective is to study determinants of the development, health and socialisation of children from birth to adulthood, using a multidisciplinary approach. The cohort is conducted using a two-stage random stratified sampling design, stratified for maternity units and for selected days. A total of 349 maternity units were randomly selected from across metropolitan France, and the children were recruited at birth from the 320 maternity units that agreed to participate. Recruitment took place during 25 days in 2011, grouped into four periods over the year (April 1 - April 4, June 27 - July 4, September 27 - October 4 and November 28 - December 5). Inclusion criteria were single or twin live births at ≥ 33 weeks of gestation, mother ≥ 18 years old with no plan to leave metropolitan France within 3 years, and informed consent signed by either both parents or just the mother, with the father being informed of his right to deny consent for participation (Charles et al., 2020). A total of 18,329 mother-child pairs were recruited.

Biological samples, including hair, were collected at birth from women at a subsample of 154 maternity units (of 211 that were eligible). These maternity units were selected for their expected number of deliveries (average > 500 deliveries per year) and their proximity (< 150 km) to the biological treatment and storage units made available by the French blood agency. Biological samples were available for women included during the last three periods of recruitment (from June to December in 2011). 2,956 maternal hair samples were collected.

Data concerning socio-demographic status, family life, parental health, behaviour and life values were collected in the course of a face-to-face interview at birth (Charles et al., 2020).

When the children were 3.5 years old, data concerning day care and school as well as child environmental exposures were collected via telephone. Home visits were specifically organised at this stage of follow-up to assess the children's cognitive function. Non-invasive biological samples (including hair) were collected from 2,044 children for whom maternal biological samples had already been collected at birth.

Assuming a hair growth rate of 1 cm per month, we selected all women who had a length of hair strand more than 7 cm, a mass of hair strand greater than or equal to 25 mg to ensure detection, and who did not live in the North East and South West areas in France (for whom hair samples were already used) (Béranger et al., 2018). OPFR concentration in the first 7 cm (proximal) from maternal hair samples allowed estimation of integrated exposure during the 7 months of pregnancy known as prenatal exposure. A total of 397 of these women had participated with their child to the neurodevelopmental follow-up at 3,5 years old with the Picture Similarities test available. Among them, 265 had a child's hair strand greater than or equal to 25 mg (length between 2cm and 10 cm). Postnatal exposure was estimated by the OPFR concentration measured from these hair samples. We then excluded seven mothers and three children for whom there was no concentration available for at least one chemical due to analytical issues. We also excluded 2 mothers and five children for whom cohort-weighting data were not available at birth and at 3.5 years, respectively. We excluded families who reported epilepsy or convulsive seizure during the first years of the child (n=1), and families with children who passed the Picture Similarities test without their required glasses (n=6).

Finally, our main sample comprised 381 families with neurodevelopmental assessment at 3.5 years of age of the child and prenatal exposure measurements, including a subsample of 250 families with additionally postnatal exposure measurements.

Hair samples and OPFR analysis

Hair strands from mothers and children were cut with scissors in the occipital region (behind the head), at the hairline, before being placed in individual envelopes and shipped to the biobank for storage at ambient temperature (Béranger et al., 2018). Hair samples were analysed by the LERES (Laboratory for Study and Research into the Environment and Health) at the French School of Public Health (EHESP, Rennes, France) by GC/MS/MS. The method developed is described elsewhere (Yon et al., 2022). Our previous work on these data (Chupeau et al., 2022) has documented pre- and post-natal exposure to 15 OPFR of children born in France in 2011 based on a prioritization ranking (Niang et al., 2019): diethyl ethyl phosphonate (DEEP), ethylhexyl diphenyl phosphate (EHDPP), tris(2-butoxyethyl) phosphate (TBEP), tri-n-butyl phosphate (TBP), tris(2-chloroethyl) phosphate (TCEP), tris(2-chloropropyl) phosphate (TCPP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), tris(2-ethylhexyl) phosphate (TEHP), triethyl phosphate (TEP), tri-m-cresyl phosphate (TMCP), trimethyl phosphate (TMP), tri-o-cresyl phosphate (TOCP), tri-isopropyl phosphate (TiPP), triphenyl phosphate (TPP) and trixylenyl phosphate (TXP). We focus in this study on 9 OPFR with detection frequency higher than 5%: EHDPP, TBEP, TBP, TCEP, TCPP, TDCPP, TEP, TMCP and TPP. The flame retardant BDE209 and BDE47, known to be associated with adverse neurodevelopment (Herbstman and Mall, 2014), were also measured in maternal hair samples but only BDE47 was measured in children hair samples for economic reasons. For some chemicals, multiple LODs was provided: the smallest LOD corresponded to the laboratory's "validated" LOD and values of the other LOD were only slightly higher, on a smaller sample size of samples, mainly explained by loss of matrices during the work, and allowing not to lose any sample.

Neurodevelopmental assessment

Children's non verbal cognitive abilities at 3.5 years were assessed with the Picture Similarities subtest from the second edition of British Ability Scale (Elliott et al., 1997). The Picture Similarities test assessed the following abilities of child : non-verbal problem solving (inductive

reasoning), visual perception and analysis, assigning meaning to a picture, developing and testing hypotheses and using verbal mediation. The test was realized with a set of 33 cards with one picture and 33 boards of 4 pictures. Each board of 4 pictures was successively presented to the child with the corresponding card, which presented a 5th picture. The child had to indicate which image on the board was to be associated with the image on the card. The first 5 boards were training boards. The test was stops as soon as the child has made 6 errors on 8 consecutive boards. The score was calculated by adding the number of correct answers (1 point per correct answer). The Picture Similarities test was studied as a continuous variable. A low score may reflect impulsivity (responding without checking the answer) (“www.pandora-elfe.inserm.fr,” 2022).

Statistical analysis

Initial weights from ELFE cohort sampling and correction for unit non-response at baseline were available for both the maternity surveys (prenatal exposures) and the 3.5-year surveys (postnatal exposures). The weighting process comprised three steps. First, we created Response Homogeneity Groups (RHGs) to reduce non-response bias. We obtained each participant’s probability of inclusion in our study. The inverse of this probability was then multiplied by the initial weight from ELFE cohort sampling. These weights were calibrated to reduce the variance of estimators with respect to the French population, using the margins of the National Perinatal Survey (ENP) (Blondel and Kermarrec, 2011). All of the following results were weighted in order to transpose more easily the results to the national French population of families with pregnant women in 2011. The unweighted results are provided in the supplementary materials.

Left-censored OPFR and BDE concentrations measured in hair samples (up to 30% of censored data) were imputed (Helsel, 2011). For each chemical, we used the maximum-likelihood estimation method (MLE) to estimate parameters of lognormal probability distribution (Helsel, 2011). These estimates were based on the set of measurements with the smallest

LOD for OPFR with multiple LODs (due to variable mass of hair). This set constituted at least 80% of the sample size for all OPFR. Then, for each LOD in each chemical, censored data were imputed by random values between 0 and the LOD from this estimated distribution (Jin et al., 2011). Imputed concentrations were log₂ transformed to obtain a normal distribution and avoid the influence of outliers. Concentrations with 50 and 70 % of detected data were transformed in factor with 3 modalities (< LOD / LOD -median / > median). Concentrations with less than 50% of detected data were transformed in factor with 2 modalities (Detected / Not detected).

The linearity between the concentrations of the OPFRs and the Picture similarities test score was respected for all OPFRs treated continuously except for TPP in children and TBP and TPP in mothers. They were therefore transformed into a factor with 4 modalities corresponding to the quartiles of the concentrations.

Associations between OPFR hair-concentrations and neurodevelopmental score were assessed by linear regression adjusted for covariates. One model per OPFR was conducted. Association of the prenatal exposure was studied in a first step on the main sample, and in a second step on the subsample adjusted on the postnatal exposure to the corresponding OPFR. Association of the postnatal exposure was reported on the subsample.

Statistical outliers responsible of the non-respect of model hypotheses, were identified according to the residual plot, the residual vs fitted value plot, the quantile plot of the residuals, cook's distance; and were then excluded in all models. 7 outliers were detected. Thus, the main final sample contained 374 mother-child pairs. In analysis of association between prenatal exposure and neurodevelopment adjusted on postnatal exposure, 6 outliers were detected. This subsample contained 244 mother-child pairs

Covariates were determined using a Directed Acyclic Graph, built within the research team after several meetings for achieving a consensus, available in supplementary material. All models were adjusted with same set of covariates, all collected at birth, including: log₂-transformed BDE209 hair-concentration, BDE47 detection (Yes/No), pre-pregnancy BMI

(<18.5, 18.5 - <25, 25-<30, >30), mother education level (high school or lower, 2 years of university level, higher than 2 years of university level) and father education level (high school or lower, 2 years of university level, higher than 2 years of university level) during pregnancy, income and mother's age at delivery. As the score of the Picture Similarities Test used in our study is not standardized on age of child, we decided to additionally adjust the models by age of the child at the Pictures Similarities testing. All covariables had less than 10% of missing data; they were thus simply imputed by the mode or the median.

SAS software 9.4 was used to impute censored data and describe OPFR concentrations. The CALMAR macro available in SAS software 9.4 was used for calibration (Deville et al., 1993). Weighted results were calculated using the SURVEY package from R software V4.0.

Ethical issues

Ethical approvals for data collection in maternity units and for each data collection wave during follow-up were obtained from the national advisory committee on information processing in health research (CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé), the national data protection authority (CNIL: Commission Nationale Informatique et Liberté) and, in case of invasive data collection such as biological sampling, the committee for protection of persons engaged in research (CPP: Comité de Protection des Personnes). The ELFE study was also approved by the national committee for statistical information (CNIS: Conseil National de l'Information Statistique) (Charles et al., 2020).

Results

Population characteristics

Characteristics of the main study sample (n=374; unweighted) and the eligible population of mothers who gave birth in France in 2011 (N=18 329, weighted results) are presented in Table 1, as well as their corresponding subpopulation for which postnatal exposure was available (n=238 and N=11 706, respectively). Mean age of mothers who gave birth in France in 2011 was 31 years (standard deviation: 7.9) at delivery, 63.1 % of them had a normal pre-pregnancy BMI (between 18.5 and 25 kg/m²). 37 % had an education level higher than baccalaureate +2 years, while for almost half of the fathers, educational attainment was below high school degree level. Mean monthly household income was 3347 euros. The score of “Picture Similarities test “for children was normally distributed, with a median 70 (IQR = 14). 54.1 % of children were boys and 45.6 % were girls.

Table 1. Characteristics of pregnant women and children included in our study, and in the French population in 2011.

Characteristics		France, 2011 (weighted results) (%)		Study sample (unweighted results) (%)	
		Population (N=18 329)	Subpopulation (N= 11 706)	Sample (n=374)	Subsample (n=238)
Mother's age at delivery (years)	Mean (s.d)	31.2 (7.9)	31.6 (8.3)	31.8 (4.7)	32.111 (4.8)
Pre-pregnancy BMI	<18.5	9.2	7.5	8.6	7.0
	18.5-<25	63.1	65.8	69.3	71.3
	25-<30	12.7	12.8	14.2	14.3
	30 or more	15.1	13.8	8.0	7.4
	<i>Missing</i>			4	
Mother's education level at delivery	High school or lower	43.5	41.8	26.2	22.5
	2 years of university level	20.2	17.4	26.2	25.0
	Higher than 2 years of university level	36.3	40.7	47.6	52.5
	<i>Missing (N)</i>	3	2	3	2
Father's education level at delivery	High school or lower	58.6	56.4	46.0	44.3
	2 years of university level	15.6	16.3	20.1	19.7
	Higher than 2 years of university level	25.8	27.3	34.0	36.1
	<i>Missing</i>			19	10
Monthly household income at delivery (euros)	Mean (s.d)	3446.6 (2235.3)	3568 (3183.5)	3726 (1864.6)	3865 (2047.2)
Sex of child	Boy	54.1	51.0	52.9	40.2
	Girl	45.6	49.0	47.1	59.8
Age of child (Months)	Mean (s.d)	41.6 (2.32)	41.4 (2.5)	41.6 (1.6)	41.4 (1.5)

Score of “Picture Smiliraties test “	Mean (s.d)	69.8 (16.7)	70.6 (18.73)	69.9 (13.4)	69.9 (13.0)
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s.d: standard deviation

Pre- and post-natal exposure to OPFR

Pre- and post-natal exposure to OPFR, estimated by OPFR concentrations measured in hair samples of mothers and children, respectively, are presented in Table 2. More detailed results are provided in our previous paper (Chupeau et al., 2022). TPP is the most commonly detected OPFR in children and in mothers: in 100% of the children's hair samples and 99.5% of the mothers' hair samples. The highest median detections were observed for TCPP in mothers and TDCPP in children.

Table 2. Pre- and post-natal exposure of children to OPFR, measured by concentrations (ng/g) in mothers' hair at birth in 2011 and in the hair of children aged 3.5 years old in 2014-2015, in France.

OPFR	CAS number	%> LOD*		Mothers Median (IQR) or %		Children Median (IQR) or %	
		Mothers	Childre n				
EHDPP	1241-94-7	92.1	94.8	35 (22-60)		75 (39-211)	
TBEP	78-51-3	25.2	50	Detected	23	<LOD	52
				No Detected	77	LOD-median	27
						>median	21
TBP	126-73-8	91.9	46.4	35 (26-45)		Detected	47
						No Detected	53
TCEP	15-96-8	60.9	68.6	<LOD	38	<LOD	31
				LOD-median	28	LOD-median	38
				>median	35	>median	31
TCPP	13674-84-5	73.5	65.5	265 (202-398)		<LOD	38
						LOD-median	34
						>median	28
TDCPP	13674-87-8	95.3	97.2	48 (20-105)		111 (41-222)	
TEP	78-40-0	95	67.5	51 (22-78)		<LOD	35
						LOD-median	36
						>median	30
TMCP	563-04-2	78	38.5	9 (5-23)		Detected	33
						No Detected	67
TPP	115-86-6	99.5	100	64 (37-110)		77 (44-144)	

* Percentages of LOD were unweighted

Association between prenatal exposure to OPFR and OPFR score of Picture Similarities test

The associations between prenatal exposure to OPFR and score of Picture similarities test are illustrated in Figures 1 and 2. All detailed results are presented in table S1 and table S2. After adjusting for covariates, we found a statistically significant decrease of 1.3 point (95% CI: -2.4, -0.2) on score of Picture similarities test per twofold increase in maternal TEP in the main population. We also observed a statistically significant decrease of 4.6 points (95% IC: -7.8; -0.6) on score of Picture similarities test for an increase of mother concentration of TBP but a statistically significant increase of 6.2 points (95% IC: 2.5; 9.9) on score of Picture similarities test for an increase of mother concentration of TPP. Associations between the Picture similarities score and six others OPFR (EHDPP, TBEP, TCPP, TCEP, TDCPP and TMCP) were negative but not statistically significant.

In the subpopulation, when taking into account the postnatal hair-measurements in the models, the association coefficients were similar but did not remain statistically significant. In addition, we found a statistically significant decrease on the score of the Picture similarities test per twofold increase in children concentration of EHDPP (-1.2; 95% IC: -2.2; -0.3) and TDCPP (-1.1; 95% IC: -2 ; -0.2) after having adjusted for prenatal exposure to the respective OPFR. We also observed a statistically significant decrease of 6 points (95% IC: -9.6; -2.3), 4.5 points (95% IC: -8.5; -0.43) and 8.7 points (95% IC: -12.81; -4.53) for an increase of children concentration of TBEP, TCEP and TPP, respectively, after adjustment on prenatal exposure.

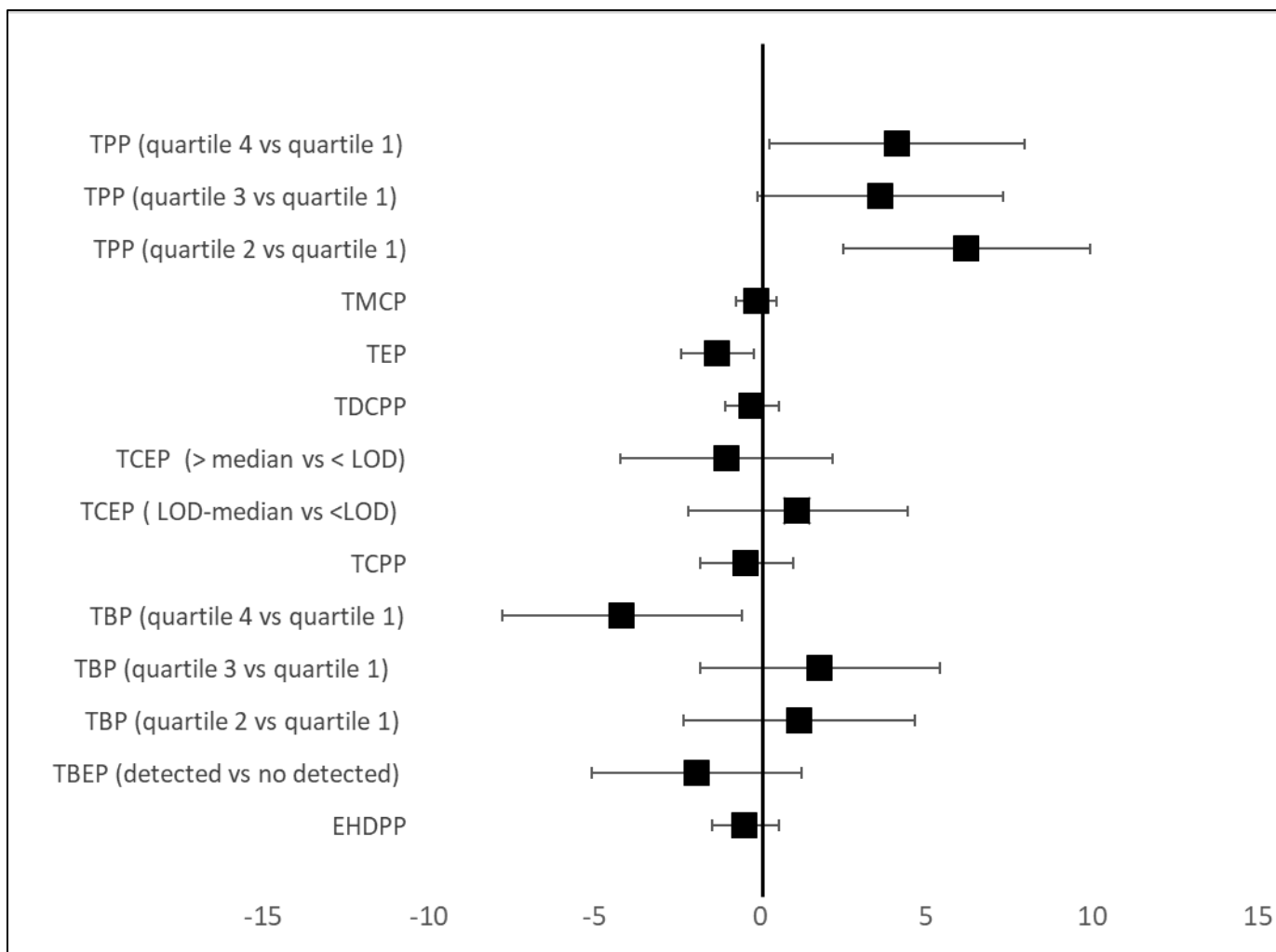


Figure 1. Associations between prenatal exposure to OPFR and score of the picture similarities test, adjusted on covariates, France 2011-2014.

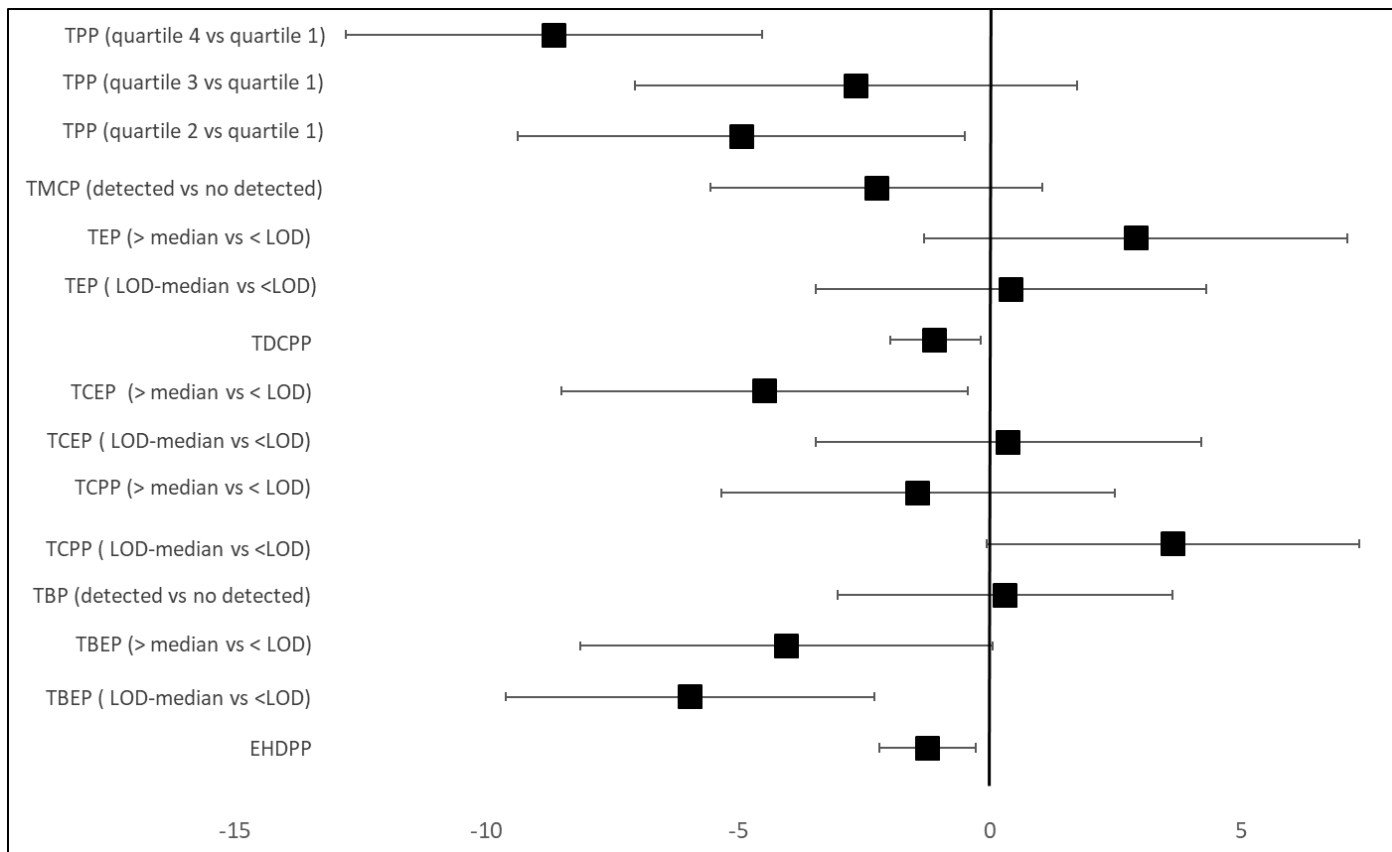


Figure 2. Associations between postnatal exposure to OPFR and score of the picture similarities test, adjusted on prenatal exposure and covariates, France 2011-2014.

Discussion

The objective of this study was to explore relationships between prenatal exposure to OPFR and non-verbal cognitive abilities at the 3.5 years old in the French population using the Elfe cohort with and without adjusting for postnatal exposure to OPFR.

Our results suggest that higher exposure to TBP and TEP during pregnancy and higher exposure to EHDPP, TBEP, TCEP, TDCPP and TPP during first years of life were associated with lower score for the Picture similarities test at 3.5-year-old children, after adjustment for potential confounders. Whereas, the effect size of prenatal exposure is low compare to the standard deviation of the Picture Similarities score which is equal to 16.7. The effect size of postnatal exposure was higher than prenatal exposure compared to the standard deviation of

the Picture Similarities which is equal to 18.7 in the subpopulation. Due to the low correlations observed between OPFR concentrations ($r < 0.5$) (Chupeau et al., 2022), we decided not to use a multipollutant model. The results for prenatal exposure to TBEP and postnatal exposure to TMCP and TBP are less robust as they are in 2 classes (detected/not detected). This may explain the absence of significance of the association.

The British Ability Scale which included the test of "Pictures similarities" is a validated tool and previously used in the Millenium cohort study at 3 and 5 years. The Picture Similarities test assesses children capacities of non-verbal resolution of problems, of visual perception and analysis, of giving signification to an image, of developing and testing an hypothesis and of using verbal mediation.

Epidemiological studies have investigated the possible neurotoxic effects associated with exposure to OPFR, particularly in children, using urine metabolites as indicators of exposure. Four studies have explored the relationship between prenatal exposure to OPFR and cognitive performance in childhood, but the findings were varying (Zhao et al., 2022). In a first US study, mothers' urine samples were collected between 24 and 29 gestation week. Children's cognitive function (Composite, Fine Motor, Visual Reception, Receptive Language, Expressive Language) was assessed using the Mullen Scales of Early Learning (MSEL), and Children's language (Vocabulary, Grammatical Complexity) was assessed using the MacArthur-Bates Communicative Development Inventories (MB-CDI) between 2 and 3 years. This study found that prenatal exposure to IP-PPP was associated with lower MSEL Cognitive Composite Score ($\beta = -2.61$; 95% CI: -5.69- 0.46), lower fine motor abilities ($\beta = -3.08$; 95% CI: -5.26, -0.91) and lower expressive language abilities ($\beta = -1.21$; 95% CI: -2.91, -0.49) (Doherty et al., 2019). Preventing from comparison with the findings of our present study that did not include this OPFR was not study in our analyses. In a second US study, mothers' urine sample were collected during the 2nd prenatal study visit. Children's cognitive abilities were assessed by a single bilingual psychometrician at age 7 using the 4th edition of the Wechsler Intelligence Scale for (WISC-IV) which evaluated Full-Scale IQ, working memory, perceptual working and

processing speed. This study found association between DPHP concentration, a metabolite of TPP, and lower score of IQ (β : -2.9; 95% CI: -6.3, -0.5) and of working memory (β : -3.9; 95% CI: -7.3,-0.5) (Castorina et al., 2017). In the present study, we found a higher score of the Picture Similarities test with increased prenatal exposure to TPP, but a lower score with increased child hair-concentrations of TPP. (Liu et al., 2021) observed a decrease in score of the mental scale which evaluated children's cognition, language and social development at 2 years of age associated with increased prenatal exposure to BDCPP, a metabolite of TDCPP, and chlorinated OPFR in boys but not in girls. In our study, we again found lower non-verbal cognitive abilities with an increase of postnatal exposure to TDCPP but not with prenatal exposure to TDCPP. In a second US study, Percy et al. looked at postnatal exposure to OPFR in relation to cognitive development during childhood and found a decrease in verbal comprehension, working memory and intelligence quotient in children from a low socio-economic background at 8 years for every log-unit increase of BDCIPP (a metabolite of TDCPP), BCEP (a metabolite of TCEP), and DPHP (a metabolite of TPHP) (Percy et al., 2022). In our study, we also found a decrease of the Picture Similarities test score with increase of postnatal exposure of these three OPFR (TDCPP, TCEP and TPP).

The present study reported association between higher prenatal exposure to TBP and a lower score of Picture Similarities test while (Percy et al., 2021) did not observe association between prenatal urinary concentration of DBP (a metabolite of TBP) and children's cognition evaluated by WISC-IV at 8 years old. No study seemed to have investigated association between prenatal exposure to TEP and children cognition.

These studies are not exactly comparable to ours because we use a different human matrix to estimate children's exposures and a different test to assess children's cognitive abilities.

Toxicological studies were conducted to investigate the neurotoxic mechanisms of OPFR exposure. To our knowledge, we have not found any toxicological study concerning the effect of prenatal exposure to TBP. Concerning postnatal exposure to TBP, its mechanism seems to be similar to chlorpyrifos with significant changes in locomotor behaviour, either in free

swimming or in photomotor response. For TEP, a prenatal exposure of this OPFR resulted in a modification in mRNA expression and a decrease in T4 in chicken eggs (Egloff et al., 2014). Developmental effect of postnatal exposure to EHDPP was observed but not neurotoxic effect. The neurotoxic effects of postnatal exposure to TBEP were evaluated in zebrafish. The studies showed a modification of the transcription of genes, some of which are involved in the synthesis of thyroid hormones, inhibition of secondary motor neuron growth. Postnatal exposure to TCEP resulted in decreased gene expression in zebrafish and impaired learning, hippocampal necrosis and decreased GABA neurotransmitter in rats. Numerous studies show a significant decrease in T4 levels and a drop in T3 levels in zebrafish after a postnatal exposure to TDCPP and TPP.

Our study has strengths but also some limitations. The first strength of our study is the wide exposure period covering pregnancy. The hair root is irrigated by blood vessels, and chemical contaminants present in the blood stream are incorporated into the internal structure of hair during hair synthesis in the scalp. Exposure information stored in hair is very stable over time, and analysis of 1 cm hair length is considered to assess average exposure over a 1-month period (Hajeb et al., 2022). Considering the human hair growth rate of 1 cm per month, and with a minimal length of 7 cm, we assessed children's OPFR exposure during at least 7 months of pregnancy with hair sample with lengths between 7 cm and 10 cm. For children, the minimal length was 2 cm and the maximal one was 10 cm. Consequently, the hair-measurements of the 3.5-year-old children may reflect various exposure windows from the previous several months to about one year. Furthermore, hair samples were measured unwashed, so OPFR concentrations may reflect both external (via deposition from air and dust) and internal (through contact with blood at the hair follicle/root). However, (Kucharska et al., 2015) found very weak or no correlation of OPFR concentrations in mothers and children's hair that it indicates that the concentrations measured in the hair of mothers and children are not driven by the (minor) amount of dust deposited onto the hair surface.

The second strength is the weighting process that enable us to correct for non-response at the various steps of the survey, to reduce the non-response bias and variance of estimators. This weighting process allowed us to give results for the population representative of the children born in 2011 in France.

Because of the smaller initial sample size of the subsample, the weighting process is more uncertain than for the main sample.

The third strength is the use of validated neurodevelopmental test. However, the score of the picture similarities test was not calculated exactly as described in the original version of the test. As a result, the test score available in Elfe does not correctly take into account the age of the child. For this reason, we decided to adjust all our models systematically to the age of the child at the time of testing. The major limitation of our study is that Elfe cohort was not designed specifically for neurodevelopmental health outcomes; therefore we assessed only this subdomain of the cognition among children. Other studies are needed to evaluate other subdomains of cognition and confirm or not these results. Another limitation is that although toxicological and epidemiological studies suggest a sex-specific effect we could not assess this effect because a split of about half of our samples did not allow us to apply the weighting process on it. Finally, we cannot exclude a classification bias due to the choice not to wash the hair, and thus an underestimation of the effect. It could occur if indoor contamination is varying over time; however, Kucharska et al. estimated that the amount of OPFR deposited on external hair is small compared to the internal amount (Kucharska et al., 2015).

Conclusion

OPFR are ubiquitous in our environment and studies found them in various human matrices. In our study, we found associations between lower non verbal cognitive abilities and increase of pre and postnatal exposure to OPFR of children. These results added to the variety of the findings of previous epidemiological studies, mostly conducted in US. This is the first study

conducted on OPFR prevalent in France. Due to the ubiquitous exposure of the general population, further studies are urgently required before drawing robust conclusion on the neurodevelopmental risks of these compounds.

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References

Bastiaensen, M., Gys, C., Malarvannan, G., Fotache, M., Bombeke, J., Ait Bamai, Y., Araki, A., Covaci, A., 2021. Short-term temporal variability of urinary biomarkers of organophosphate flame retardants and plasticizers. *Environ. Int.* 146, 106147. <https://doi.org/10.1016/j.envint.2020.106147>

Béranger, R., Hardy, E.M., Dexet, C., Guldner, L., Zaros, C., Nougadère, A., Metten, M.-A., Chevrier, C., Appenzeller, B.M.R., 2018. Multiple pesticide analysis in hair samples of pregnant French women: Results from the ELFE national birth cohort. *Environ. Int.* 120, 43–53. <https://doi.org/10.1016/j.envint.2018.07.023>

Beser, M.I., Pardo, O., Beltrán, J., Yusà, V., 2019. Determination of 21 perfluoroalkyl substances and organophosphorus compounds in breast milk by liquid chromatography coupled to orbitrap high-resolution mass spectrometry. *Anal. Chim. Acta* 1049, 123–132. <https://doi.org/10.1016/j.aca.2018.10.033>

Blondel, B., Kermarrec, M., 2011. Les naissances en 2010 et leur évolution en 2003.

Blum, A., Behl, M., Birnbaum, L.S., Diamond, M.L., Phillips, A., Singla, V., Sipes, N.S., Stapleton, H.M., Venier, M., 2019. Organophosphate Ester Flame Retardants: Are They a Regrettable Substitution for Polybrominated Diphenyl Ethers? *Environ. Sci. Technol. Lett.* 6, 638–649. <https://doi.org/10.1021/acs.estlett.9b00582>

Castorina, R., Bradman, A., Stapleton, H.M., Butt, C., Avery, D., Harley, K.G., Gunier, R.B., Holland, N., Eskenazi, B., 2017. Current-use flame retardants: Maternal exposure and neurodevelopment in children of the CHAMACOS cohort. *Chemosphere* 189, 574–580. <https://doi.org/10.1016/j.chemosphere.2017.09.037>

Charles, M.A., Thierry, X., Lanoe, J.-L., Bois, C., Dufourg, M.-N., Popa, R., Cheminat, M., Zaros, C., Geay, B., 2020. Cohort Profile: The French national cohort of children (ELFE): birth to 5 years. *Int. J. Epidemiol.* 49, 368–369j. <https://doi.org/10.1093/ije/dyz227>

Choi, G., Keil, A.P., Richardson, D.B., Daniels, J.L., Hoffman, K., Villanger, G.D., Sakhi, A.K., Thomsen, C., Reichborn-Kjennerud, T., Aase, H., Engel, S.M., 2021. Pregnancy exposure to organophosphate esters and the risk of attention-deficit hyperactivity disorder in the Norwegian mother, father and child cohort study. *Environ. Int.* 154, 106549. <https://doi.org/10.1016/j.envint.2021.106549>

Chupeau, Z., Bonvallot, N., Mercier, F., Le Bot, B., Chevrier, C., Glorennec, P., 2020. Organophosphorus Flame Retardants: A Global Review of Indoor Contamination and Human

Exposure in Europe and Epidemiological Evidence. *Int. J. Environ. Res. Public Health* 17, 6713. <https://doi.org/10.3390/ijerph17186713>

Chupeau, Z., Mercier, F., Rouxel, E., Le Bot, B., Chauvet, G., Siméon, T., Bonvallot, N., Zaros, C., Chevrier, C., Glorennec, P., 2022. Pre- and post-natal exposure of children to organophosphate flame retardants: A nationwide survey in France. *Environ. Int.* 168, 107435. <https://doi.org/10.1016/j.envint.2022.107435>

Crawford, K.A., Hawley, N., Calafat, A.M., Jayatilaka, N.K., Froehlich, R.J., Has, P., Gallagher, L.G., Savitz, D.A., Braun, J.M., Werner, E.F., Romano, M.E., 2020. Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. *Environ. Health* 19, 1–12. <https://doi.org/10.1186/s12940-020-00648-0>

Deville, J.-C., Särndal, C.-E., Sautory, O., 1993. Generalized Raking Procedures in Survey Sampling. *J. Am. Stat. Assoc.* 88, 1013–1020. <https://doi.org/10.1080/01621459.1993.10476369>

Ding, J., Xu, Z., Huang, W., Feng, L., Yang, F., 2016. Organophosphate ester flame retardants and plasticizers in human placenta in Eastern China. *Sci. Total Environ.* 554–555, 211–217. <https://doi.org/10.1016/j.scitotenv.2016.02.171>

Doherty, B.T., Hoffman, K., Keil, A.P., Engel, S.M., Stapleton, H.M., Goldman, B.D., Olshan, A.F., Daniels, J.L., 2019. Prenatal exposure to organophosphate esters and cognitive development in young children in the Pregnancy, Infection, and Nutrition Study. *Environ. Res.* 169, 33–40. <https://doi.org/10.1016/j.envres.2018.10.033>

Egloff, C., Crump, D., Porter, E., Williams, K.L., Letcher, R.J., Gauthier, L.T., Kennedy, S.W., 2014. Tris(2-butoxyethyl)phosphate and triethyl phosphate alter embryonic development, hepatic mRNA expression, thyroid hormone levels, and circulating bile acid concentrations in chicken embryos. *Toxicol. Appl. Pharmacol.* 279, 303–310. <https://doi.org/10.1016/j.taap.2014.06.024>

Gu, Y., Yang, Y., Wan, B., Li, M., Guo, L.-H., 2018. Inhibition of O-linked N-acetylglucosamine transferase activity in PC12 cells – A molecular mechanism of organophosphate flame retardants developmental neurotoxicity. *Biochem. Pharmacol.* 152, 21–33. <https://doi.org/10.1016/j.bcp.2018.03.017>

Hajeb, P., Castaño, A., Cequier, E., Covaci, A., López, M.E., Antuña, A.G., Haug, L.S., Henríquez-Hernández, L.A., Melymuk, L., Pérez Luzardo, O., Thomsen, C., Vorkamp, K., 2022. Critical review of analytical methods for the determination of flame retardants in human matrices. *Anal. Chim. Acta* 1193, 338828. <https://doi.org/10.1016/j.aca.2021.338828>

Helsel, D.R., 2011. *Statistics for Censored Environmental Data Using Minitab and R*. John Wiley & Sons.

Herbstman, J.B., Mall, J.K., 2014. Developmental Exposure to Polybrominated Diphenyl Ethers and Neurodevelopment. *Curr. Environ. Health Rep.* 1, 101–112. <https://doi.org/10.1007/s40572-014-0010-3>

Hoffman, K., Daniels, J.L., Stapleton, H.M., 2014. Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. *Environ. Int.* 63, 169–172. <https://doi.org/10.1016/j.envint.2013.11.013>

- Jin, Y., Hein, M.J., Deddens, J.A., Hines, C.J., 2011. Analysis of Lognormally Distributed Exposure Data with Repeated Measures and Values below the Limit of Detection Using SAS. *Ann. Occup. Hyg.* 55, 97–112. <https://doi.org/10.1093/annhyg/meq061>
- Kemmlein, S., Hahn, O., Jann, O., 2003. Emissions of organophosphate and brominated flame retardants from selected consumer products and building materials. *Atmos. Environ.* 37, 5485–5493. <https://doi.org/10.1016/j.atmosenv.2003.09.025>
- Kucharska, A., Cequier, E., Thomsen, C., Becher, G., Covaci, A., Voorspoels, S., 2015. Assessment of human hair as an indicator of exposure to organophosphate flame retardants. Case study on a Norwegian mother-child cohort. *Environ. Int.* 83, 50–57. <https://doi.org/10.1016/j.envint.2015.05.015>
- Lipscomb, S.T., McClelland, M.M., MacDonald, M., Cardenas, A., Anderson, K.A., Kile, M.L., 2017. Cross-sectional study of social behaviors in preschool children and exposure to flame retardants. *Environ. Health* 16, 23. <https://doi.org/10.1186/s12940-017-0224-6>
- Liu, W., Luo, D., Xia, W., Tao, Y., Wang, L., Yu, M., Hu, L., Zhou, A., Covaci, A., Lin, C., Xu, S., Mei, S., Li, Y., 2021. Prenatal exposure to halogenated, aryl, and alkyl organophosphate esters and child neurodevelopment at two years of age. *J. Hazard. Mater.* 408, 124856. <https://doi.org/10.1016/j.jhazmat.2020.124856>
- Liu, X., Cai, Y., Wang, Y., Xu, S., Ji, K., Choi, K., 2019. Effects of tris(1,3-dichloro-2-propyl) phosphate (TDCPP) and triphenyl phosphate (TPP) on sex-dependent alterations of thyroid hormones in adult zebrafish. *Ecotoxicol. Environ. Saf.* 170, 25–32. <https://doi.org/10.1016/j.ecoenv.2018.11.058>
- Liu, Y., Wu, D., Xu, Q., Yu, L., Liu, C., Wang, J., 2017. Acute exposure to tris (2-butoxyethyl) phosphate (TBOEP) affects growth and development of embryo-larval zebrafish. *Aquat. Toxicol.* 191, 17–24. <https://doi.org/10.1016/j.aquatox.2017.07.015>
- Niang, B., Glorennec, P., Bot, B.L., Mercier, F., Chevrier, C., Bonvallot, N., 2019. Hiérarchisation de contaminants anthropiques semi-volatils pour l'étude des risques. Le cas des retardateurs de flamme organophosphorés. *Environ. Risques Santé* 18, 222–234. <https://doi.org/10.1684/ers.2019.1309>
- Pantelaki, I., Voutsas, D., 2021. Organophosphate esters in inland and coastal waters in northern Greece. *Sci. Total Environ.* 800, 149544. <https://doi.org/10.1016/j.scitotenv.2021.149544>
- Patisaul, H.B., Behl, M., Birnbaum, L.S., Blum, A., Diamond, M.L., Rojello, F.S., Hogberg, H.T., Kwiatkowski, C.F., Page, J.D., Soehl, A., Stapleton, H.M., 2021. Beyond Cholinesterase Inhibition: Developmental Neurotoxicity of Organophosphate Ester Flame Retardants and Plasticizers. *Environ. Health Perspect.* 129, 105001. <https://doi.org/10.1289/EHP9285>
- Percy, Z., Chen, A., Yang, W., Braun, J.M., Lanphear, B., Ospina, M., Calafat, A.M., Xie, C., Cecil, K.M., Vuong, A.M., Xu, Y., Yolton, K., 2022. Childhood urinary organophosphate esters and cognitive abilities in a longitudinal cohort study. *Environ. Res.* 215, 114265. <https://doi.org/10.1016/j.envres.2022.114265>
- Percy, Z., Vuong, A.M., Xu, Y., Xie, C., Ospina, M., Calafat, A.M., Lanphear, B.P., Braun, J.M., Cecil, K.M., Dietrich, K.N., Chen, A., Yolton, K., 2021. Prenatal exposure to a mixture of organophosphate esters and intelligence among 8-year-old children of the HOME Study. *NeuroToxicology* 87, 149–155. <https://doi.org/10.1016/j.neuro.2021.09.005>

- Rock, K.D., St Armour, G., Horman, B., Phillips, A., Ruis, M., Stewart, A.K., Jima, D., Muddiman, D.C., Stapleton, H.M., Patisaul, H.B., 2020. Effects of Prenatal Exposure to a Mixture of Organophosphate Flame Retardants on Placental Gene Expression and Serotonergic Innervation in the Fetal Rat Brain. *Toxicol. Sci.* 176, 203–223. <https://doi.org/10.1093/toxsci/kfaa046>
- Stapleton, H.M., Klosterhaus, S., Eagle, S., Fuh, J., Meeker, J.D., Blum, A., Webster, T.F., 2009. Detection of Organophosphate Flame Retardants in Furniture Foam and U.S. House Dust. *Environ. Sci. Technol.* 43, 7490–7495. <https://doi.org/10.1021/es9014019>
- Stapleton, H.M., Sharma, S., Getzinger, G., Ferguson, P.L., Gabriel, M., Webster, T.F., Blum, A., 2012. Novel and high volume use flame retardants in US couches reflective of the 2005 PentaBDE phase out. *Environ. Sci. Technol.* 46, 13432–13439. <https://doi.org/10.1021/es303471d>
- Sundkvist, A.M., Olofsson, U., Haglund, P., 2010. Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. *J. Environ. Monit. JEM* 12, 943–951. <https://doi.org/10.1039/b921910b>
- van der Veen, I., de Boer, J., 2012. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere* 88, 1119–1153. <https://doi.org/10.1016/j.chemosphere.2012.03.067>
- Wang, Q., Liang, K., Liu, J., Yang, L., Guo, Y., Liu, C., Zhou, B., 2013. Exposure of zebrafish embryos/larvae to TDCPP alters concentrations of thyroid hormones and transcriptions of genes involved in the hypothalamic–pituitary–thyroid axis. *Aquat. Toxicol.* 126, 207–213. <https://doi.org/10.1016/j.aquatox.2012.11.009>
- Wei, G.-L., Li, D.-Q., Zhuo, M.-N., Liao, Y.-S., Xie, Z.-Y., Guo, T.-L., Li, J.-J., Zhang, S.-Y., Liang, Z.-Q., 2015. Organophosphorus flame retardants and plasticizers: Sources, occurrence, toxicity and human exposure. *Environ. Pollut.* 196, 29–46. <https://doi.org/10.1016/j.envpol.2014.09.012>
- www.flameretardants-online.com, 2022. The flame retardants market | FLAMERETARDANTS-ONLINE [WWW Document]. www.flameretardants-online.com. URL <https://www.flameretardants-online.com/flare-retardants/market> (accessed 6.7.22).
- www.pandora-elfe.inserm.fr [WWW Document], 2022. . www.pandora-elfe.inserm.fr. URL <https://pandora.vjf.inserm.fr/public/> (accessed 5.30.18).
- Yang, Y., Chen, P., Ma, S., Lu, S., Yu, Y., An, T., 2022. A critical review of human internal exposure and the health risks of organophosphate ester flame retardants and their metabolites. *Crit. Rev. Environ. Sci. Technol.* 52, 1528–1560. <https://doi.org/10.1080/10643389.2020.1859307>
- Yon, T., Saramito, G., Lecorgne, A., Goyat, Q., Glorennec, P., Bot, B.L., Mercier, F., 2022. Simultaneous determination of organophosphorus and brominated flame retardants and polychlorinated biphenyls in hair by pressurized liquid extraction and gas chromatography/tandem mass spectrometry. <https://doi.org/10.26434/chemrxiv-2022-ng6d8>
- Zhao, J., Zhan, Z., Lu, M., Tao, F., Wu, D., Gao, H., 2022. A systematic scoping review of epidemiological studies on the association between organophosphate flame retardants and neurotoxicity. *Ecotoxicol. Environ. Saf.* 243, 113973. <https://doi.org/10.1016/j.ecoenv.2022.113973>

CHAPITRE 4 : Discussion générale et Conclusion

4. Discussion générale

4.1. Synthèse des principaux résultats

Ce travail de thèse a permis pour la première fois en France d'estimer, dans un premier temps, les expositions pré et post-natales des enfants français aux RFOP ainsi que d'étudier les déterminants de cette exposition, puis, dans un second temps, d'étudier les effets neurotoxiques possibles associés à ces substances chez les enfants grâce à des mesures de concentrations de RFOP dans les cheveux des femmes enceintes et des enfants au sein de la cohorte Elfe. Chez les femmes enceintes, 8 RFOP ont été détectés dans plus de 60 % des femmes et 6 RFOP ont été détectés à plus de 60 % chez les enfants avec le TPHP détecté chez tous les enfants. La médiane de concentration la plus élevée a été observée pour le TCPP chez les enfants et chez les femmes enceintes ; environ 250 ng/g. Notons que ces concentrations restent plus faibles que les concentrations en mercure (neurotoxique reconnu) mesurées aussi dans les cheveux de la population française.

Les corrélations observées entre les RFOP entre les deux périodes de vie considérées étaient faibles ; ceci suggérerait que les sources d'exposition sont variables et/ou peuvent évoluer dans le temps que l'adulte (femme enceinte) et l'enfant pourraient ne pas être exposés aux mêmes sources, ou encore que l'absorption et la biodisponibilité des RFOP vers les cheveux varient entre la femme enceinte et l'enfant. De même les corrélations entre les concentrations des RFOP mesurées dans les cheveux des enfants et les poussières des maisons étaient faibles, suggérant pour ces RFOP que la poussière ne serait pas une source prépondérante d'exposition ; ce qui semble ne pas être concordant avec la majorité des études précédentes réalisées dans un contexte européen.

Les déterminants majeurs des expositions prénatales aux RFOP étaient l'IMC pré-grossesse la réalisation de travaux de rénovation dans l'année précédant l'accouchement ainsi que les expositions prénatales aux BDE 209 et 47. Les déterminants majeurs des expositions postnatales étaient le revenu mensuel, le niveau d'étude de la maman à l'accouchement ainsi que l'exposition prénatal au BDE 47.

Enfin, concernant l'étude des effets délétères sur le neurodéveloppement de l'enfant possiblement associés à l'exposition à ces substances, des associations statistiquement significatives ont été observées entre l'exposition prénatale au TNBP et au TEP et des capacités cognitives non verbales plus faibles chez les enfants à 3.5 ans ainsi que des associations statistiquement significatives entre l'exposition postnatale aux RFOP suivants : EHDPP, TBEP, TCEP, TDCPP et TPP et une baisse des performances cognitives non verbales chez les enfants à 3.5 ans ajusté sur l'exposition prénatale

4.2. Comparaison des résultats avec la littérature

Une seule autre étude, norvégienne, a mesuré les concentrations des RFOP chez des femmes enceintes et leurs enfants. Les concentrations mesurées étaient du même ordre de grandeur que les concentrations mesurées dans notre étude, excepté pour le TBEP dont la concentration médiane était 6 fois plus élevée chez les enfants norvégiens que chez les enfants français. Plusieurs études épidémiologiques se sont intéressées aux effets neurotoxiques possibles associés à l'exposition périnatale au RFOP, en particulier chez les enfants. Quatre études ont exploré la relation entre l'exposition prénatale aux RFOP et les performances cognitives dans l'enfance, mais les conclusions étaient variées (Zhao et al., 2022). Une étude américaine s'est intéressée à l'exposition postnatale aux RFOP en lien avec le développement cognitif durant l'enfance concluant à une diminution de la compréhension verbale, de la mémoire de travail et du quotient intellectuel chez les enfants issus d'un milieu socio-économique défavorisé (Percy et al., 2022). Cependant, l'ensemble de ces études épidémiologiques ont mesuré les RFOP dans les urines et non dans les cheveux ce qui rend les résultats difficilement comparables avec nos travaux. Des études toxicologiques réalisées sur les rongeurs ont montré qu'une exposition in utero aux RFOP étaient neurotoxiques via un processus non cholinergique incluant la perturbation du glutamate, de l'acide gamma aminobutyric (GABA) et une perturbation du système endocrinien. Ces études ne vont pas dans le sens de l'hypothèse initiale d'un effet neurotoxique via un processus cholinergique similaire aux pesticides organophosphorés. D'autres études toxicologiques sont donc

nécessaires pour confirmer ces résultats et mieux comprendre les mécanismes biologiques sous-jacents.

4.3. Considérations méthodologiques

4.3.1. Imputation des données de concentration sous la limite de détection

Comme souvent en expologie et épidémiologie environnementale, une partie des données d'exposition était censurée, i.e. avec une concentration indéterminée, car inférieure à la limite de quantification et/ou de détection, et a dû être imputée. Plusieurs méthodes existent pour l'imputation des données censurées à gauche. La première méthode est d'exclure les individus pour lesquels il y a des données censurées. La seconde méthode est la méthode substitution qui consiste à remplacer les données sous la limite de détection (LOD) par une valeur fixe : 0, 0.5, LOD/2, LOD/ $\sqrt{2}$, $\sqrt{\text{LOD}}$. Cependant, ces deux premières méthodes donnent des estimateurs biaisés. D'autres méthodes ont été développées pour limiter le biais, dont la méthode d'estimation du maximum de vraisemblance (MLE). Selon Jin et al., 2011, cette dernière donne des résultats moins biaisés que les deux premières même jusqu'à 80 % de données censurées. Il existe également la méthode de Kaplan-Meier (KM). C'est une méthode non paramétrique qui fait l'hypothèse que l'ensemble des données (censurées et non censurées) sont issues de la même pollution. Elle ne requiert pas d'hypothèse d'une distribution spécifique et a été initialement créée pour analyser les données censurées à droite dans les données de survie. Elle est recommandée pour les échantillons de taille inférieure à 50 avec moins de 50 % de données censurées et l'existence de multiple limite de détection. Une autre méthode qui existe est la régression robuste sur les statistiques d'ordre (Robust regression on order statistics (ROS)). La méthode ROS est une méthode semi-paramétrique qui est basée sur l'utilisation de modèle de régression linéaire et la distribution des quantiles pour estimer les données censurées. Elle fait l'hypothèse que la variable de concentration est une fonction linéaire de la distribution normale (ou log normal) des quantiles de cette variable.

Elle est recommandée pour des échantillons de taille supérieure à 50 individus avec moins de 50 % de données censurées et la présence de multiples limites de détection et pour les échantillons d'effectifs inférieurs à 50 avec moins de 80 % de données censurées et la présence de multiples limites de détection. Les données imputées sont utilisées pour les descriptions statistiques des données de concentrations, mais elles ne peuvent pas être extraites pour être utilisées par la suite dans des analyses plus complexes (par exemple : des analyses d'associations). Il n'est pas possible de connaître la valeur imputée d'un individu en particulier pour une substance. Les méthodes de KM et ROS donnent également des estimateurs non biaisés, mais n'étaient pas appropriés dans notre cas. En effet, tout d'abord, nous avons des échantillons de taille supérieure à 50 avec des pourcentages de données censurées allant jusqu'à 80 %. De plus, il était nécessaire de pouvoir extraire les données imputées pour les utiliser dans nos modèles de régression d'analyses de déterminants et d'association entre les expositions pré- et post-natale aux RFOP et le développement cognitif de l'enfant. Enfin, nous avons plusieurs limites de détection pour une même substance. Nous avons donc utilisé la méthode MLE. C'est une méthode paramétrique qui fait l'hypothèse que les données censurées et non censurées suivent une distribution statistique donnée (normal, log-normal, weibull, gamma etc.). Au regard de la distribution de nos données non censurées, nous avons décidé de choisir une hypothèse de distribution log-normale. De précédentes études ont également fait le choix de cette distribution (Kucharska et al., 2015 ; Liu et al., 2021 ; Percy et al., 2022). Les paramètres sont les estimateurs qui maximisent la fonction de vraisemblance après avoir défini la distribution des données. Si l'hypothèse de distribution est correcte, la méthode MLE donne des estimateurs précis et sans biais. Elle est recommandée pour des tailles d'échantillon supérieures à 50 avec moins de 80 % de données censurées et la présence de plusieurs seuils de détection est possible (Helsel, 2011 ; Mancin et al., 2017).

4.3.2. Redressement des échantillons

Pour que nos résultats soient extrapolables à notre population cible Elfe (femmes enceintes et enfants nés en 2011), nous avons redressé, au moyen de poids de sondage, notre échantillon

d'études afin qu'il soit similaire à notre population cible. Lorsqu'une ou plusieurs enquêtes au cours d'une étude doivent être réalisées en face-à-face, mais que la population est dispersée, et afin de limiter les déplacements des enquêteurs, on sélectionne un échantillon parmi tous les individus. Pour cela, des méthodes d'échantillonnage (ou plans de sondages) à plusieurs degrés sont utilisées. Dans Elfe, un échantillonnage à deux (maternité, jours) degrés a été réalisé avec tout d'abord, une sélection aléatoire de maternités françaises puis une sélection aléatoire de jours. Tous les bébés nés dans les maternités et les jours sélectionnés ont été enquêtés (Juillard, 2016).

Dans une enquête, il existe deux types de non-réponse : la non-réponse totale et la non-réponse partielle. Lorsque aucune information n'est relevée concernant un individu inclus dans l'étude, de la « non-réponse totale » est produite. Lorsque seulement une partie de l'information est relevée concernant un individu inclus dans l'étude, cela produit de la « non-réponse partielle ». La correction de la non-réponse se fait grâce aux informations auxiliaires connues sur l'ensemble de l'échantillon et qui soit explicative de la probabilité de répondre à l'enquête et / ou explicative de la variable d'intérêt (dans notre cas, les variables d'intérêts étaient les expositions aux RFOP). La non-réponse totale conduit à un sous-échantillon de répondants. La non-réponse totale est habituellement traitée par une méthode de repondération (Kim et Kim, 2007) en supprimant du fichier les non-répondants totaux puis en augmentant les poids des répondants par l'inverse des probabilités estimées pour compenser la non-réponse totale. Le poids des répondants sont créées grâce à une modélisation du mécanisme aléatoire conduisant à notre sous-échantillon de répondants. La modélisation se fait en deux étapes. La première étape correspond à modéliser la sélection de notre échantillon initiale et la seconde étape correspond à modéliser le mécanisme de réponse des répondants conduisant à notre sous-échantillon des répondants. Un modèle expliquant la non-réponse totale couramment utilisé consiste à supposer que la probabilité de réponse p_i est constante au sein de groupes partitionnant notre échantillon initial. Ces groupes sont appelés « Groupes Homogènes de Réponses » (GHR). Ils peuvent être constitués de la façon suivante : on effectue une régression logistique afin d'expliquer les probabilités de réponses p_i en fonction

des informations auxiliaires disponibles puis on ne garde que les informations auxiliaires expliquant les probabilités de réponses. Le croisement des modalités de ces variables auxiliaires donne les GHR. Au sein de chaque GHR, la probabilité de réponse est égale au nombre de répondants de ce groupe sur le nombre total d'individus du groupe (Chauvet, 2017).

Pour nos analyses, les poids de sondages ont été créés en deux étapes. Tout d'abord, les probabilités de réponse (=probabilité d'être inclus dans nos échantillons) ont été calculées à l'aide de GHR. Puis, nous avons corrigé les poids de sondage créée dans Elfe pour chaque enquête en multipliant les poids de sondage disponible dans Elfe par l'inverse de nos probabilités d'inclusions calculées à la première étape. Cette méthode s'appelle une pondération par la probabilité inverse (IPW). Puis, les poids obtenus ont été calés, par une étape de calage, sur différentes variables socio-démographiques. La première étape de pondération par IPW vise à réduire les biais liés à la non-réponse. La seconde étape de calage vise à réduire la variance des estimateurs en ajustant les poids sur des totaux liés aux variables d'intérêt (Chauvet, 2019).

4.4. Forces et limites

La plus grande force de ce travail est que l'ensemble de ces résultats ont pu être présentés sur la population française des femmes enceintes et des enfants français en 2011 grâce aux processus de redressement de nos échantillons permettant d'obtenir des échantillons représentatifs de la population française métropolitaine. La seconde force de nos analyses est l'utilisation de la cohorte Elfe qui nous a permis d'estimer une exposition des enfants sur deux périodes importantes pour leur développement : les périodes pré et post-natales grâce au design mère-enfant de l'étude. La troisième force de ce travail est la période d'exposition couverte qui est de minimum 7 mois de grossesse pour la période prénatale et de maximum 10 mois pour la période postnatale. La première limite de ce travail est un biais de classification que nous ne pouvons pas exclure dû au choix de ne pas réaliser d'étape de lavage des échantillons de cheveux pouvant entraîner une surestimation de l'exposition. La seconde limite

concerne les résultats des déterminants des expositions. Ils sont à interpréter avec précaution, notamment en termes de complétude des déterminants. En effet, la cohorte Elfe n'a pas été spécialement conçue pour les expositions environnementales et ainsi plusieurs déterminants retrouvés dans la littérature comme la fréquence de nettoyage ou le nombre de meubles dans la maison n'ont pu être inclus dans notre étude. D'autres études sont nécessaires pour mieux identifier les déterminants et ainsi conduire à la mise en place de mesures de prévention afin de réduire l'exposition aux RFOP de la population française et en particulier des populations potentiellement vulnérables comme les femmes enceintes et les jeunes enfants. La dernière limite est l'absence d'analyse stratifiée sur le sexe de l'enfant, malgré des études toxicologiques suggérant un effet différentiel selon le sexe, dû à un nombre insuffisant d'enfants inclus dans notre étude.

4.5. Perspectives

Cette étude rapporte une prévalence forte, voire ubiquitaire, des expositions aux RFOP et montre un effet défavorable possible de ces substances sur la cognition de l'enfant. Mais c'est la première étude en France s'intéressant à ces questions. D'autres études sont donc nécessaires pour confirmer ces résultats afin de mettre en place des politiques de prévention des expositions aux RFOP si elles s'avéraient nécessaires, tout en tenant compte des avantages de RFOP pour prévenir les incendies. Il est également nécessaire de s'assurer par des études complémentaires que les concentrations mesurées dans les cheveux reflètent correctement les doses de RFOP présentes dans le corps humain.

L'utilisation de la matrice cheveux pour estimer les expositions aux substances chimiques des populations a plusieurs avantages : la collecte de cheveux est non-invasive, c'est une matrice simple à conserver et à transporter et elle permet l'estimation d'une exposition sur une longue période. Cependant, il n'a pas encore été démontré si les concentrations mesurées dans les cheveux reflétaient correctement les concentrations de RFOP mesurées dans le sang. En effet, la métabolisation des RFOP par le corps humain n'a pas encore été décrite. De

nombreuses questions subsistent concernant le stockage et la variabilité des RFOP dans le cheveu, le transfert des RFOP entre le sang et le cheveu, le transfert entre le sang maternel et le placenta puis le cordon ombilical ainsi que le processus de diffusion des RFOP dans l'organisme du fœtus. Comment les RFOP atteignent le cerveau du fœtus ? Sont-ils seulement véhiculés par le sang ? Il y a-t-il des RFOP dans le liquide amniotique ? Il est donc nécessaire de réaliser des études complémentaires pour décrire la métabolisation de ces substances par l'organisme. En complément, il serait intéressant d'étudier les corrélations entre les concentrations de RFOP mesurées dans les cheveux et les concentrations mesurées dans d'autres matrices d'une même maman (sang, urines, liquide amniotique, sang de cordon). Des mesures des RFOP pourraient également être réalisées dans le méconium. Ces études complémentaires permettraient d'apporter des éléments de réponses à la question de la matrice à choisir pour estimer au mieux l'exposition des RFOP de la population.

Des études toxicologiques sont également nécessaires pour mieux comprendre le mécanisme d'action des RFOP sur le corps humain. En effet, de récentes études suggèrent un effet neurotoxique des RFOP via un processus non cholinergique. Ces études ne vont pas dans le sens de l'hypothèse initiale d'un effet neurotoxique via un processus cholinergique similaire aux pesticides organophosphorés.

Nos travaux ne se sont intéressés que à un domaine de la cognition, ce qui limite la portée de l'interprétation de ces résultats. Il serait également important de s'intéresser aux capacités verbales, à la mémoire, à l'apprentissage ou à la cognition sociale de l'enfant. D'autres études peuvent être réalisées grâce aux données de la cohorte Elfe. En effet, à 2 ans, le test « Mac Arthur Communicative Inventories » mesure le développement du langage de l'enfant et à 5.5 ans le test « Strengths and Difficulties Questionnaire (SDQ) » évalue le comportement de l'enfant.

Les RFOP halogénés comme le TCEP, le TCPP ou le TDCPP sont majoritairement utilisés dû à la présence d'un atome de chlore qui augmente la durée de vie du retardateur de flamme dans le produit final en diminuant sa mobilité. Le TCPP représente approximativement 80 %

des RFP chlorés en Europe et c'est le RFP le plus utilisé en Europe (en volume) dans les années 2000 (van der Veen and de Boer, 2012). Or, dans notre étude, c'est le retardateur mesuré en plus forte concentration chez les mamans et chez les enfants. Il est principalement utilisé dans les mousses de polyuréthane et se retrouve donc dans les meubles rembourrés type canapé. Le TDCPP est aussi utilisé dans les mousses de polyuréthane, mais aussi dans les textiles et le plastique. Le TCEP a des utilisations plus diverses comme le PVC, la cellulose les résines de polyester mais est aussi utilisé dans les mousses de polyuréthane. Il serait intéressant dans les prochaines études de se focaliser sur cette famille de retardateurs de flamme et en particulier sur le TCPP.

5. Conclusion

Ce travail de thèse a permis de mettre en évidence une exposition généralisée des enfants aux retardateurs de flammes organophosphorés à la fois in utero mais aussi au cours des premières années de vie de l'enfant. Il a également permis de montrer qu'une exposition pré et post-natale à certains RFOP était associée à des performances cognitives non verbales plus faibles à 3.5 ans. En France, c'est la première étude qui s'intéresse à l'exposition des femmes enceintes et des enfants aux RFOP et à leurs effets néfastes potentiels sur le neuro-développement. Les perspectives d'études dans ce domaine sont nombreuses. Il est donc important de poursuivre les travaux notamment pour les générations futures.

Bibliographie

Abou-Elwafa Abdallah, M., Pawar, G., Harrad, S., 2016. Human dermal absorption of chlorinated organophosphate flame retardants; implications for human exposure. *Toxicol. Appl. Pharmacol.* 291, 28-37. <https://doi.org/10.1016/j.taap.2015.12.004>

Ait Bamai, Y., Araki, A., Nomura, T., Kawai, T., Tsuboi, T., Kobayashi, S., Miyashita, C., Takeda, M., Shimizu, H., Kishi, R., 2018. Association of filaggrin gene mutations and childhood eczema and wheeze with phthalates and phosphorus flame retardants in house dust: The Hokkaido study on Environment and Children's Health. *Environ. Int.* 121, 102-110. <https://doi.org/10.1016/j.envint.2018.08.046>

Araki, A., Bastiaensen, M., Ait Bamai, Y., Van den Eede, N., Kawai, T., Tsuboi, T., Ketema, R.M., Covaci, A., Kishi, R., 2018. Associations between allergic symptoms and phosphate flame retardants in dust and their urinary metabolites among school children. *Environ. Int.* 119, 438-446. <https://doi.org/10.1016/j.envint.2018.07.018>

Barker, D.J., Osmond, C., Law, C.M., 1989. The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. *J. Epidemiol. Community Health* 43, 237-240.

Bellinger, D.C., 2012. Comparing the population neurodevelopmental burdens associated with children's exposures to environmental chemicals and other risk factors. *NeuroToxicology, Neurotoxicity and Neurodegeneration: Local Effect and Global Impact* 33, 641-643. <https://doi.org/10.1016/j.neuro.2012.04.003>

Bellinger, D.C., 2008. Very low lead exposures and children's neurodevelopment. *Curr. Opin. Pediatr.* 20, 172-177. <https://doi.org/10.1097/MOP.0b013e3282f4f97b>

Beser, M.I., Pardo, O., Beltrán, J., Yusà, V., 2019. Determination of 21 perfluoroalkyl substances and organophosphorus compounds in breast milk by liquid chromatography coupled to orbitrap high-resolution mass spectrometry. *Anal. Chim. Acta* 1049, 123-132. <https://doi.org/10.1016/j.aca.2018.10.033>

Castorina, R., Bradman, A., Stapleton, H.M., Butt, C., Avery, D., Harley, K.G., Gunier, R.B., Holland, N., Eskenazi, B., 2017a. Current-use flame retardants: Maternal exposure and neurodevelopment in children of the CHAMACOS cohort. *Chemosphere* 189, 574-580. <https://doi.org/10.1016/j.chemosphere.2017.09.037>

Castorina, R., Butt, C., Stapleton, H.M., Avery, D., Harley, K.G., Holland, N., Eskenazi, B., Bradman, A., 2017b. Flame retardants and their metabolites in the homes and urine of pregnant women residing in California (the CHAMACOS cohort). *Chemosphere* 179, 159-166. <https://doi.org/10.1016/j.chemosphere.2017.03.076>

Chauvet, G., 2019. Weighting in Sample Surveys Application to the ELFE data.

Chauvet, G., 2017. Estimation en situation de non-réponse dans une enquête de cohorte.

Chupeau, Z., Bonvallot, N., Mercier, F., Le Bot, B., Chevrier, C., Glorennec, P., 2020. Organophosphorus Flame Retardants: A Global Review of Indoor Contamination and Human Exposure in Europe and Epidemiological Evidence. *Int. J. Environ. Res. Public. Health* 17, 6713. <https://doi.org/10.3390/ijerph17186713>

Chupeau, Z., Mercier, F., Rouxel, E., Le Bot, B., Chauvet, G., Siméon, T., Bonvallot, N., Zaros, C., Chevrier, C., Glorennec, P., 2022. Pre- and post-natal exposure of children to organophosphate flame retardants: A nationwide survey in France. *Environ. Int.* 168, 107435. <https://doi.org/10.1016/j.envint.2022.107435>

Comprendre REACH [WWW Document], n.d. URL <https://echa.europa.eu/fr/regulations/reach/understanding-reach> (accessed 10.11.22).

de Boer, J., Ballesteros-Gómez, A., Leslie, H.A., Brandsma, S.H., Leonards, P.E.G., 2016. Flame retardants: Dust - And not food - Might be the risk. *Chemosphere* 150, 461-464. <https://doi.org/10.1016/j.chemosphere.2015.12.124>

Des Portes, V., 2020. Troubles du neurodéveloppement: aspects cliniques. *Contraste* 51, 21-53. <https://doi.org/10.3917/cont.051.0021>

Doherty, B.T., Hoffman, K., Keil, A.P., Engel, S.M., Stapleton, H.M., Goldman, B.D., Olshan, A.F., Daniels, J.L., 2019. Prenatal exposure to organophosphate esters and cognitive development in young children in the Pregnancy, Infection, and Nutrition Study. *Environ. Res.* 169, 33-40. <https://doi.org/10.1016/j.envres.2018.10.033>

Etude longitudinale française depuis l'enfance [WWW Document], 2021. URL https://pandora-elfe.inserm.fr/doc/20210924_E3A_protocole_domicile_FR_JLL_ACv1.pdf (accessed 10.10.22).

Farías, P., Hernández-Bonilla, D., Moreno-Macías, H., Montes-López, S., Schnaas, L., Texcalac-Sangrador, J.L., Ríos, C., Riojas-Rodríguez, H., 2022. Prenatal Co-Exposure to Manganese, Mercury, and Lead, and Neurodevelopment in Children during the First Year of Life. *Int. J. Environ. Res. Public Health* 19, 13020. <https://doi.org/10.3390/ijerph192013020>

George, A., Hansen, K., Schoon, I., 2007. Millenium Cohort Study. Cognitive development. Taken from Chapter 7 of Millenium Cohort Study Second Survey: A User's Guide to Initial Findings. [WWW Document]. URL <https://cls.ucl.ac.uk/wp-content/uploads/2017/06/1Cognitive-AMENDED-230707.pdf> (accessed 11.23.22).

Helsel, D.R., 2011. *Statistics for Censored Environmental Data Using Minitab and R*. John Wiley & Sons.

Hoffman, K., Daniels, J.L., Stapleton, H.M., 2014. Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. *Environ. Int.* 63, 169-172. <https://doi.org/10.1016/j.envint.2013.11.013>

Inserm. Pesticides et effets sur la santé: Nouvelles données. Collection Expertise collective. Montrouge: EDP Sciences, 2021. Pesticides et effets sur la santé-Nouvelles données (Rapport de recherche), Isabelle Baldi, Botton Jérémie, Cécile Chevrier, Xavier Coumoul, Alexis Elbaz, et al.. Pesticides et effets sur la santé: Nouvelles données. [Rapport de recherche] Inserm (dir.). Pesticides et effets sur la santé - Nouvelles données. Collection Expertise collective. Montrouge: EDP Sciences, 2021., Institut national de la santé et de la

recherche médicale (INSERM). 2021, Paris : Inserm : Editions EDP Sciences (ISSN: 0990-7440) / XIX - 1009 p. inserm-03384960f.

Jin, Y., Hein, M.J., Deddens, J.A., Hines, C.J., 2011. Analysis of Lognormally Distributed Exposure Data with Repeated Measures and Values below the Limit of Detection Using SAS. *Ann. Occup. Hyg.* 55, 97-112. <https://doi.org/10.1093/annhyg/meq061>

Juillard, H., 2016. Two-dimensional sampling in practice 14.

Kucharska, A., Cequier, E., Thomsen, C., Becher, G., Covaci, A., Voorspoels, S., 2015. Assessment of human hair as an indicator of exposure to organophosphate flame retardants. Case study on a Norwegian mother-child cohort. *Environ. Int.* 83, 50-57. <https://doi.org/10.1016/j.envint.2015.05.015>

Liu, W., Luo, D., Xia, W., Tao, Y., Wang, L., Yu, M., Hu, L., Zhou, A., Covaci, A., Lin, C., Xu, S., Mei, S., Li, Y., 2021. Prenatal exposure to halogenated, aryl, and alkyl organophosphate esters and child neurodevelopment at two years of age. *J. Hazard. Mater.* 408, 124856. <https://doi.org/10.1016/j.jhazmat.2020.124856>

Llop, S., Guxens, M., Murcia, M., Lertxundi, A., Ramon, R., Riaño, I., Rebagliato, M., Ibarluzea, J., Tardon, A., Sunyer, J., Ballester, F., on Behalf of the INMA Project, 2012. Prenatal Exposure to Mercury and Infant Neurodevelopment in a Multicenter Cohort in Spain: Study of Potential Modifiers. *Am. J. Epidemiol.* 175, 451-465. <https://doi.org/10.1093/aje/kwr328>

Mancin, M., Barco, L., Ricci, A., 2017. Statistical methods to estimate the assigned value in presence of multiple censored results [WWW Document]. URL https://www.eurachem.org/images/stories/workshops/2017_10_PT/pdf/contrib/O05-Mancin.pdf (accessed 11.23.22).

Meeker, J.D., Cooper, E.M., Stapleton, H.M., Hauser, R., 2013. Urinary Metabolites of Organophosphate Flame Retardants: Temporal Variability and Correlations with House Dust Concentrations. *Environ. Health Perspect.* 121, 580-585. <https://doi.org/10.1289/ehp.1205907>

Meeker, J.D., Stapleton, H.M., 2010. House Dust Concentrations of Organophosphate Flame Retardants in Relation to Hormone Levels and Semen Quality Parameters. <https://doi.org/10.1289/ehp.0901332>

Negrell, C., Ménard, R., 2016. Retardateurs de flamme phosphorés commerciaux pour les polymères. *Phys. Chim.* <https://doi.org/10.51257/a-v1-af6047>

Niang, B., Glorennec, P., Bot, B.L., Mercier, F., Chevrier, C., Bonvallot, N., 2019. Hiérarchisation de contaminants anthropiques semi-volatils pour l'étude des risques. Le cas des retardateurs de flamme organophosphorés. *Environ. Risques Santé* 18, 222-234. <https://doi.org/10.1684/ers.2019.1309>

Patisaul, H.B., Behl, M., Birnbaum, L.S., Blum, A., Diamond, M.L., Rojello, F.S., Hogberg, H.T., Kwiatkowski, C.F., Page, J.D., Soehl, A., Stapleton, H.M., 2021. Beyond Cholinesterase Inhibition: Developmental Neurotoxicity of Organophosphate Ester Flame Retardants and Plasticizers. *Environ. Health Perspect.* 129, 105001. <https://doi.org/10.1289/EHP9285>

Percy, Z., Chen, A., Yang, W., Braun, J.M., Lanphear, B., Ospina, M., Calafat, A.M., Xie, C., Cecil, K.M., Vuong, A.M., Xu, Y., Yolton, K., 2022. Childhood urinary organophosphate esters and cognitive abilities in a longitudinal cohort study. *Environ. Res.* 215, 114265. <https://doi.org/10.1016/j.envres.2022.114265>

Pinfa, 2017. FLAME RETARDANTS IN ELECTRIC AND ELECTRONIC APPLICATIONS [WWW Document]. URL https://www.pinfa.eu/wp-content/uploads/2018/05/PINFA_EE_brochure_Edition_2017-11.pdf (accessed 10.11.22).

Retardateurs de flamme bromés | EFSA [WWW Document], n.d. URL <https://www.efsa.europa.eu/fr/topics/topic/brominated-flame-retardants> (accessed 10.11.22).

Siméon, T., 2019. PONDERATIONS DES ENQUETES NATIONALES. [WWW Document]. URL https://pandora-elfe.inserm.fr/doc/Pond%C3%A9rations_enqu%C3%AAtes_nationales.pdf (accessed 12.2.22).

Stapleton, H.M., Klosterhaus, S., Eagle, S., Fuh, J., Meeker, J.D., Blum, A., Webster, T.F., 2009. Detection of Organophosphate Flame Retardants in Furniture Foam and U.S. House Dust. *Environ. Sci. Technol.* 43, 7490-7495. <https://doi.org/10.1021/es9014019>

van der Veen, I., de Boer, J., 2012. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere* 88, 1119-1153. <https://doi.org/10.1016/j.chemosphere.2012.03.067>

Zhao, J., Zhan, Z., Lu, M., Tao, F., Wu, D., Gao, H., 2022. A systematic scoping review of epidemiological studies on the association between organophosphate flame retardants and neurotoxicity. *Ecotoxicol. Environ. Saf.* 243, 113973. <https://doi.org/10.1016/j.ecoenv.2022.113973>

Annexes

Annexe: Matériel supplémentaire de l'article « Organophosphorus Flame Retardants: A Global Review of Indoor Contamination and Human Exposure in Europe and Epidemiological Evidence ».



Supplementary Table S1. OPFRs abbreviation.

CAS Number	Used Acronym	Commonly Used Acronym	International Name	Metabolite Used Acronym	Metabolite Commonly Used Acronym	International Name	Others Metabolite
38051-10-4	BCMP-BCEP	V6, TCDDP	Tetrakis (2-chlorethyl) dichloroisopentyl diphosphate				
5945-33-5	BDP	BADP, BAPP, BPADP, BPA-BDPP	Bisphenol-A diphenyl phosphate				
2752-95-6	BdPhP		Butyl diphenyl phosphate				
2528-36-1	dBPhP		Dibutyl phenyl phosphate				
838-85-7	DPP	DPK	Diphenylphosphate				
1241-94-7	EHDPP	EDP, EHDP, EHDPP, DPEHP, EHDPHP	Ethylhexyldiphényl phosphate				5-HO-EHDPHP, EHPHP
29761-21-5	iDDPHP	IDDP, IDPP	Isodecyldiphenylphosphate				
249-828-6	iDPP		Isodecyl diphenyl phosphate				
	IIP	IPTP, IPTPP	Isopropylated triarylphosphate esters	IP-PPP		Isopropylphenyle phenyl phosphate	tb-PPP
57583-54-7	PBDPP	RDP	Resorcinol-bis (diphenyl) phosphate				
78-51-3	TBOEP	TBEP, TBXP	Tris (2-butoxyethyl) phosphate	BBOEP		Bis(2-butoxyethyl) phosphate	3-HO-TBEP
				BBOEHEP		Bis(2-butoxyethyl)-(2-hydroxyethyl) phosphate	
				DBOEP	DBEP	Di-(2-butoxyethyl) phosphate	
78-33-1	TBPP	TBDP	Tris (p-t-butylphenyl) phosphate				
115-96-8	TCEP		Tris (2-chloroethyl) phosphate	BCEP		Bis-(2-chlorethyl)-phosphate	uTCEP
				DCEP		Di-(2-chloroethyl) phosphate	
13674-84-5	TCIPP	TCPP, TCiPP	Dris(2-chloroisopropyl)phosphate	BCIPP	BCPP	Bis(1-chloro-2-propyl) phosphate	BCIPHIPP
				DCIPP	DCPP	Di-(2-chloroisopropyl) phosphate	
126-72-7	TDBPP	TDBP, TDB99	Tris (2,3-Dibromopropyl) phosphate				
13674-87-8	TDCIPP	TDCPP, TDCiPP	Tris(1,3-dichloro-2-propyl) phosphate	BDCIPP	BDCPP	Bis(1,3-dichloro-2-propyl) phosphate	
78-42-2	TEHP	TOF, TOP	Tris (2-ethylhexyl) phosphate	DEHP		Diethylhexyl phosphate	BEHP
78-40-0	TEP		Triethyphosphate	DEP		Diethyl phosphate	
2528-39-4	THP		Trihexyl phosphate				
2528-39-4	THP		Trihexyl phosphate				
126-71-6	TIBP	TiBP, TiP	Tri-iso-butylphosphate				
513-02-0	TIPP	TIPrP, TiPP, TiPrP	Tri-isopropylphosphate				
64532-95-2	TiPPP	o-IPP, T2IPPP	Phenol isopropylated phosphate, ortho				
563-04-2	TmCP		Tri-m-cresylphosphate	DmCP		Di-m-cresyl phosphate	
512-56-1	TMP	TMPA, TMPO	Trimethylphosphate				

1330-78-5	TMPP	TCrP, TTOP, TTP, TBT, TCP, TBT	Tricresylphosphate (mixture o, m, p)							DMPP
126-73-8	TNBP	TnBP, TBP, TB	Tri-n-butylphosphate	DnBP	DBP					Di-n-butyl phosphate
78-30-8	ToCP	TOCP, TOTP, o-TCP, o-TMPP	Tri-o-cresylphosphate	DoCP						Di-o-cresyl phosphate
78-32-0	TpCP	TPCP, p-TCP	Tri-p-cresylphosphate	DpCP						Di-p-cresyl phosphate
2528-38-3	TPEP		Triphenylphosphate							
115-86-6	TPHP	TPP, TPhP	Triphenylphosphate	DPHP	DPP					Diphenyl phosphate
513-08-6	TPP	TnPP, TPrP, TPPO, TnPrP	Tri-n-propylphosphate							4-HO-DPHP, 3-HO-TPHP, 4-HO-TPHP
25653-16-1	TXP	TDMPP	Tris(3,5-xilylenyl)phosphate							

Supplementary Table S2. Concentrations of OPFRs in indoor dust (µg/g), Europe, 2000-2018.

CAS number	Abbreviation	Period	Country	Sampling Location	Sample Size	Min.	Max.	Mean	Median	References
38051-10-4	BCMP-BCEP	2013	UK	Homes	10	0	0.76	0.1	0.02	Kademoglou et al.,2017
		2013-2014	Norway	Homes	10	0	0.01	0	0	Kademoglou et al.,2018
		-	Greece	Cars	25	0	8.54	0.68	0.01 *	Christia et al.,2018
5945-33-5	BDP	2013	UK	Homes	10	<0.0034	0.49	0.12	0.07	Kademoglou et al.,2017
		2013-2014	Norway	Homes	10	<0.0034	0.7	0.12	-	Kademoglou et al.,2017
		-	Greece	Cars	25	0	0.42	0.04	0.02 *	Christia et al.,2018
838-85-7	DPP	2016	The netherlands	Homes (on top of electronics)	11	0.22	6.59	2.78	2.58	Björnsdotter et al., 2018
		2016	The netherlands	Homes and Offices	12	0.15	4.19	1.2	0.74	Björnsdotter et al., 2018
		2017	Spain	Cars	15	0.92	79.66	8.29	2.31	Björnsdotter et al., 2018
		2017	Spain	Homes (on top of electronics)	13	0.3	21.9	3.21	1.75	Björnsdotter et al., 2018
1241-94-7	EHDPP	2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<0.14	540	-	2.1	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<0.14	11	-	<014	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	<0.23	20	-	2.7	Luongo and Östman.,2016
		2010-2011	Portugal	Homes	28	0.15	7.2	1.1	0.62	Coelho et al.,2016
		2011-2012	Germany	Dayecare centers	63	0.3	95.6	4.13	1.1	Fromme et al.,2014
		2011-2012	Germany	Cars	19	0.01	1.8	-	1.2	Harrad et al.,2016
		2011-2012	Germany	Homes (living rooms)	22	<0.01	0.56	-	0.14	Harrad et al.,2016
		2011-2012	Germany	Offices	25	0.13	3.8	-	0.36	Harrad et al.,2016
		2011-2012	UK (West Midlands)	Cars	21	0.29	11	2.9	2.2	Brommer and Harrad.,2015
		2011-2012	UK (West Midlands)	Classroom	28	0.3	470	50	29	Brommer and Harrad.,2015
		2011-2012	UK (West Midlands)	Homes (living room)	32	0.18	130	2.6	1.6	Brommer and Harrad.,2015
		2011-2012	UK (West Midlands)	Offices	61	0.15	0.05	81	10	Brommer and Harrad.,2015
		2012	Norway	Homes	48	-	5.9	0.88	0.62	Cequier et al.,2014
		2013	Czech Republic	Homes	30	0.14	8.23	-	0.84	Vykoukalová et al.,2017
		2013	UK	Homes	10	0.29	9.17	3.01	2.38	Kademoglou et al.,2017
		2013-2014	Norway	Homes	10	0.04	4.01	0.74	0.2	Kademoglou et al.,2017
2013-2014	Norway (Oslo)	Homes (floor)	61	0.083	12.5	-	0.42	Xu et al.,2016		
2013-2014	Norway (Oslo)	Homes (surface)	61	0.212	30.2	-	0.455	Xu et al.,2016		
-	Sweden (Stockolm)	Daycare center	10	0.2	160	24	0.8	Bergh et al.,2011		

		-	Sweden (Stockolm)	Homes	10	N.D	1.8	0.6	0.5	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	N.D	73	15	1	Bergh et al.,2011
29761-21-5	iDDPHP	-	Greece	Cars	25	0.04	4.63	0.36	0.12 *	Christia et al.,2018
249-828-6	iDPP	2013	UK	Homes	10	0.11	1.69	0.62	0.4	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	0.01	0.26	0.08	0.05	Kademoglou et al.,2017
57583-54-7	PBDPP	2013	UK	Homes	10	<0.0018	0	0	0	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	<0.0018	<0.0018	<0.0018	<0.0018	Kademoglou et al.,2017
		-	Greece	Cars	25	0	0.65	0.04	0.004 *	Christia et al.,2018
78-51-3	TBOEP	2008	Swenden (Stockolm)	Homes	62	<0.20	107	-	11	Luongo and Östman.,2016
		2008	Belgium	Homes (floor)	33	0.2	55.7	11.8	3.61	Van den Eede et al.,2011
		2008	Belgium	Shop	15	0.2	55.7	11.8	3.61	Van den Eede et al.,2011
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<0.40	11000	-	26	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<0.40	1300	-	<0.40	Langer et al.,2016
		2010	Roumania (Lasi)	Homes	47	<0.05	21	2.7	1.5	Dirtu et al.,2012
		2010–2011	Germany	Cars	12	<0.06	74	21	7.5	Brommer et al.,2012
		2010–2011	Germany	Offices	10	2.9	13	7	-	Brommer et al.,2012
		2011–2012	Germany	Dayecare centers	63	1.61	4711	706	225	Fromme et al.,2014
		2012	Norway	Homes	48	-	128	18.7	13.4	Cequier et al.,2014
		2013	UK	Homes	10	0.23	58.75	16.08	8.07	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	1.34	48.01	19.15	18.36	Kademoglou et al.,2017
		2013–2014	Norway (Oslo)	Homes (floor)	61	0.73	311	-	8.15	Xu et al.,2016
		2013–2014	Norway (Oslo)	Homes (surface)	61	<0.090	540	-	6.8	Xu et al.,2016
		2015	Germany (Rhine/Main area)	Cars	11	2.3	200	35	7.5	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	2.1	99	13	4.3	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	4.8	150	45	8.6	Zhou et al.,2017
		-	Greece	Cars	25	0.19	9.78	1.41	0.90 *	Christia et al.,2018
		-	Sweden (Stockolm)	Daycare center	10	31	4100	1900	1600	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	0.6	30	8.5	4	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	4.5	960	250	87	Bergh et al.,2011
78-33-1	TBPP	2013	Czech Republic	Homes	30	0	0.04	-	0.01	Vykoukalová et al.,2017
115-96-8	TCEP	2005	Austria	Schools	34	0.6	35	-	2.5	Huuter et al.,2013
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<0.6	1800	-	16	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<0.60	230	-	6.9	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	<0.19	808	-	4	Luongo and Östman.,2016
		2008	Belgium	Homes (floor)	33	<0.08	2.65	0.49	0.23	Van den Eede et al.,2011
		2008	Belgium	Shop	15	<0.08	5.46	1.17	0.59	Van den Eede et al.,2011
		2010	Roumania (Lasi)	Homes	47	<0.02	1.16	0.18	0.1	Dirtu et al.,2012
		2010–2011	Germany	Cars	12	<0.08	5.8	0.95	0.28	Brommer et al.,2012
		2010–2011	Germany	Offices	10	<0.08	0.17	0.12	-	Brommer et al.,2012
		2010–2011	Portugal	Homes	28	<0.004	0.72	0.06	0.02	Coelho et al.,2016
		2011–2012	UK (West Midlands)	Cars	21	<0.06	8.7	1.95	1.23	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Classroom	28	<0.06	8.3	1.5	0.86	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Homes (living room)	32	<0.06	28	2.2	0.81	Brommer and Harrad.,2015

		2011–2012	UK (West Midlands)	Offices	61	<0.06	160	5	0.87	Brommer and Harrad.,2015
		2011–2012	Germany	Daycare centers	63	0.1	8.3	1.35	0.4	Fromme et al.,2014
		2011–2012	Germany	Cars	19	<0.06	5.1	-	0.4	Harrad et al.,2016
		2011–2012	Germany	Homes (living rooms)	22	<0.06	5.7	-	0.21	Harrad et al.,2016
		2011–2012	Germany	Offices	25	<0.06	12	-	0.13	Harrad et al.,2016
		2012	Norway	Homes	48	-	4.63	0.8	0.41	Cequier et al.,2014
		2013	UK	Homes	10	0.14	6.27	1.57	0.87	Kademoglou et al.,2017
		2013	Czech Republic	Homes	30	0.04	1.68	-	0.16	Vykoukalová et al.,2017
		2013–2014	Norway	Homes	10	0.06	0.5	0.74	0.2	Kademoglou et al.,2017
		2013–2014	Norway (Oslo)	Homes (floor)	61	<0.170	350	-	0.435	Xu et al.,2016
		2013–2014	Norway (Oslo)	Homes (surface)	61	<0.170	15.2	-	0.455	Xu et al.,2016
		2013–2015	Netherlands	Homes (playroom)	50	0.02	5.66	-	0.16	Sugeng et al.2018
		2015	Germany (Rhine/Main area)	Cars	11	<LOD	170	18	1.4	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	<LOD	5	1.3	1.1	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	0.93	18	3.7	1.9	Zhou et al.,2017
		-	Sweden (Stockolm)	Daycare center	10	2.5	150	51	30	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	N.D	33	7.6	2.1	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	1.3	260	36	6.7	Bergh et al.,2011
		-	Greece	Cars	25	0.01	13.14	1.24	0.11 *	Christia et al.,2018
13674-84-5	TCIPP	2008	Belgium	Homes (floor)	33	0.19	73.7	4.82	1.38	Van den Eede et al.,2011
		2008	Belgium	Shop	15	0.58	24.4	5.16	2.94	Van den Eede et al.,2011
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<1.10	350	-	5.6	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<1.10	100	-	<1,10	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	1.21	98	-	11	Luongo and Östman.,2016
		2010	Roumania (Lasi)	Homes	47	<0.02	16.4	2.5	0.86	Dirtu et al.,2012
		2010–2011	Germany	Cars	12	1.4	4.3	3.1	3.2	Brommer et al.,2012
		2010–2011	Germany	Offices	10	0.18	9.4	3	-	Brommer et al.,2012
		2011–2012	Germany	Dayecare centers	63	0.71	47	4.65	2.68	Fromme et al.,2014
		2011–2012	Germany	Cars	19	0.29	100	-	2.9	Harrad et al.,2016
		2011–2012	Germany	Homes (living rooms)	22	0.33	5.7	-	1	Harrad et al.,2016
		2011–2012	Germany	Offices	25	0.18	13	-	1.6	Harrad et al.,2016
		2011–2012	UK (West Midlands)	Cars	21	2.4	370	83	53	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Classroom	28	1.7	210	33	16	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Homes (living room)	32	3.7	100	29	21	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Offices	61	3.6	230	44	33	Brommer and Harrad.,2015
		2012	Norway	Homes	48	-	40.1	5.74	2.68	Cequier et al.,2014
		2013	Czech Republic	Homes	30	0.16	26.7	-	1.86	Vykoukalová et al.,2017
		2013–2014	Norway (Oslo)	Homes (surface)	61	<0.055	498	-	5.24	Xu et al.,2016
		2013–2014	Norway (Oslo)	Homes (floor)	61	<0.055	145	-	2	Xu et al.,2016
		2013–2015	Netherlands	Homes (playroom)	50	0.14	0.03	-	0.83	Sugeng et al.2018
		2015	Germany (Rhine/Main area)	Cars	11	4	340	41	7.8	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	1.7	10	5	4.2	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	1.8	470	52	8.5	Zhou et al.,2017

		-	Greece	Cars	25	0.11	101.8	8.06	2.61 *	Christia et al.,2018
		-	Sweden (Stockolm)	Daycare center	10	0.8	12	4.5	3.1	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	0.7	11	3.1	1.6	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	3.4	120	32	19	Bergh et al.,2011
126-72-7	TDBPP	2013	UK	Homes	10	<0.0005	0	0	<0,0005	Kademoglou et al.,2017
		2013	Czech Republic	Homes	30	N.D	N.D	-	N.D	Vykoukalová et al.,2017
		2013–2014	Norway	Homes	10	0	0.02	0.01	0	Kademoglou et al.,2017
13674-87-8	TDCIPP	2008	Belgium	Homes (floor)	33	<0.08	6.64	0.57	0.36	Van den Eede et al.,2011
		2008	Belgium	Shop	15	<0.08	56.2	4.61	0.76	Van den Eede et al.,2011
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<1.20	320	-	7.1	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<1.20	860	-	<1,20	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	<0.60	12	-	2	Luongo and Östman.,2016
		2010	Roumania (Lasi)	Homes	47	<0.02	0.46	0.1	0.06	Dirtu et al.,2012
		2010–2011	Germany	Cars	12	<0.08	620	130	21	Brommer et al.,2012
		2010–2011	Germany	Offices	10	<0.08	0.29	0.15	-	Brommer et al.,2012
		2010–2011	Portugal	Homes	28	<0.0018	0.39	0.06	0.02	Coelho et al.,2016
		2011–2012	Germany	Cars	19	<0.03	620	-	4.1	Harrad et al.,2016
		2011–2012	Germany	Homes (living rooms)	22	<0.03	14	-	0.08	Harrad et al.,2016
		2011–2012	Germany	Offices	25	<0.03	2.2	-	0.14	Harrad et al.,2016
		2011–2012	UK (West Midlands)	Cars	21	0.11	740	110	31	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Classroom	28	0.04	10	1.1	0.51	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Homes (living room)	32	0.06	14	2	0.71	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Offices	61	<0.03	51	2.1	0.48	Brommer and Harrad.,2015
		2012	Norway	Homes	48	-	6.92	0.8	0.5	Cequier et al.,2014
		2013	Czech Republic	Homes	30	0.06	1.22	-	0.18	Vykoukalová et al.,2017
		2013	UK	Homes	10	0.35	3.79	1.08	0.75	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	0.08	2.31	0.51	0.34	Kademoglou et al.,2017
		2013–2014	Norway (Oslo)	Homes (floor)	61	<0.055	6	-	0.4	Xu et al.,2016
		2013–2014	Norway (Oslo)	Homes (surface)	61	<0.055	366	-	1.13	Xu et al.,2016
		2013–2015	Netherlands	Homes (playroom)	50	0.03	0.01	-	0.7	Sugeng et al.2018
		2015	Germany (Rhine/Main area)	Cars	11	3	56	16	4.7	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	<LOD	4.3	0.85	<LOD	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	0.8	39	6.3	3.2	Zhou et al.,2017
		-	Greece	Cars	25	0.02	85.04	7.52	2.51 *	Christia et al.,2018
		-	Sweden (Stockolm)	Daycare center	10	3.9	150	28	9.1	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	2.2	27	12	10	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	3.3	91	30	17	Bergh et al.,2011
78-42-2	TEHP	2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<2.50	3.8	-	<2.50	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<2.50	11	-	<2.50	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	<2.10	46	-	<2.10	Luongo and Östman.,2016
		2010–2011	Portugal	Homes	28	0.25	2.3	2.2	1.7	Coelho et al.,2016
		2011–2012	Germany	Daycare centers	63	<0.30	4.85	0.68	0.5	Fromme et al.,2014
		2013	Czech Republic	Homes	30	0.04	10.3	-	0.15	Vykoukalová et al.,2017

		2013	UK	Homes	10	0.1	0.47	0.22	0.16	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	0.11	0.62	0.24	0.18	Kademoglou et al.,2017
		2013–2014	Norway (Oslo)	Homes (floor)	61	<0.140	3.98	-	0.4	Xu et al.,2016
		2013–2014	Norway (Oslo)	Homes (surface)	61	<0.140	450	-	0.71	Xu et al.,2016
		2015	Germany (Rhine/Main area)	Cars	11	0.7	14	3.1	2	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	<LOD	2.1	0.14	<LOD	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	<LOD	1.4	0.43	<LOD	Zhou et al.,2017
		-	Sweden (Stockolm)	Daycare center	10	N.D	0.7	0.2	0.1	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	N.D	0.2	N.D	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	N.D	0.3	0.1	N.D	Bergh et al.,2011
78-40-0	TEP	2008	Belgium	Homes (floor)	33	N.D	N.D	<0.05	<0.05	Van den Eede et al.,2011
		2008	Belgium	Shop	15	<0.05	0.37	0.13	0.06	Van den Eede et al.,2011
		2008	Swenden (Stockolm)	Homes	62	<0.03	4.3	-	0.19	Luongo and Östman.,2016
		2010	Romania (Lasi)	Homes	47	<0.01	0.42	0.03	0.02	Dirtu et al.,2012
		2015	Germany (Rhine/Main area)	Cars	11	0.2	4.2	0.99	0.44	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	<LOD	2.3	0.31	<LOD	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	0.25	4.3	0.82	0.42	Zhou et al.,2017
		-	Sweden (Stockolm)	Daycare center	10	N.D	4.7	0.7	0.2	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	N.D	N.D	N.D	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	N.D	0.3	0.1	0.1	Bergh et al.,2011
2528-39-4	THP	2008	Swenden (Stockolm)	Homes	62	<0.03	5.8	-	<0.30	Luongo and Östman.,2016
126-71-6	TIBP	2008	Belgium	Homes (floor)	33	0.7	15.6	4.2	2.99	Van den Eede et al.,2011
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<0.03	2.5	-	<0.03	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<0.03	37	-	<0,03	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	<0.02	47	-	5.3	Luongo and Östman.,2016
		2010	Roumania (Lasi)	Homes	47	<0.10	2.39	0.4	0.39	Dirtu et al.,2012
		2011–2012	Germany	Daycare centers	63	<0.30	8.3	0.77	<0.30	Fromme et al.,2014
		2015	Germany (Rhine/Main area)	Cars	11	0.28	2.3	0.75	0.51	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	<LOD	0.82	0.37	0.38	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	0.31	1.3	0.68	0.66	Zhou et al.,2017
		-	Sweden (Stockolm)	Daycare center	10	0.5	1.5	0.9	0.7	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	0.4	3.6	1.4	1.1	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	0.5	9.2	2.4	1.3	Bergh et al.,2011
513-02-0	TIPP	2008	Swenden (Stockolm)	Homes	62	<0.02	0.4	-	<0.02	Luongo and Östman.,2016
64532-95-2	TiPPP	2013	Czech Republic	Homes	30	0	0.51	-	0.01	Vykoukalová et al.,2017
1330-78-5	TMPP	2008	Belgium	Homes (floor)	33	<0.04	5.07	0.44	0.24	Van den Eede et al.,2011
		2008	Belgium	Shop	15	<0.04	12.5	1.53	0.2	Van den Eede et al.,2011
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<0.89	36	-	<0.89	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<0.89	18	-	<0.89	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	<0.49	31	-	2.7	Luongo and Östman.,2016
		2010	Roumania (Lasi)	Homes	47	<0.05	5.5	1	0.5	Dirtu et al.,2012
		2010–2011	Portugal	Homes	28	0.02	0.48	0.13	0.1	Coelho et al.,2016
		2011–2012	Germany	Cars	12	<0.04	150	24	1.2	Brommer et al.,2012

		2011–2012	Germany	Offices	10	<0.04	1.9	0.37	-	Brommer et al.,2012
		2011–2012	Germany	Cars	19	<0.01	150	-	0.86	Harrad et al.,2016
		2011–2012	Germany	Homes (living rooms)	22	<0.01	1.3	-	0.14	Harrad et al.,2016
		2011–2012	Germany	Offices	25	<0.01	1.9	-	1.9	Harrad et al.,2016
		2011–2012	UK (West Midlands)	Cars	21	<0.01	5.6	1	0.59	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Classroom	28	<0.01	5.8	0.05	<0.01	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Homes (living room)	32	<0.01	14	2	0.02	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Offices	61	<0.01	5.3	0.33	<0.01	Brommer and Harrad.,2015
		2012	Norway	Homes	48	-	16.2	1.12	0.31	Cequier et al.,2014
		2013	UK	Homes	10	0.08	1.05	0.46	0.29	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	0.11	3.18	0.5	0.19	Kademoglou et al.,2017
		2013–2014	Norway (Oslo)	Homes (dust)	61	<0.020	30.1	-	0.33	Xu et al.,2016
		2013–2014	Norway (Oslo)	Homes (floor)	61	<0.020	7.52	-	0.18	Xu et al.,2016
		2013–2015	Netherlands	Homes (playroom)	50	0	3.99	-	0.21	Sugeng et al.2018
		2015	Germany (Rhine/Main area)	Cars	11	<LOD	120	14	2.3	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	<LOD	3.3	0.43	<LOD	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	<LOD	48	8.2	0.34	Zhou et al.,2017
		-	Greece	Cars	25	0.02	0.88	0.15	0.03 *	Christia et al.,2018
		-	Sweden (Stockolm)	Daycare center	10	N.D	13	2	0.4	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	N.D	3	1.2	1	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	N.D	2.9	0.8	0.6	Bergh et al.,2011
126-73-8	TNBP	2008	Belgium	Homes (floor)	33	0.03	2.7	0.25	0.13	Van den Eede et al.,2011
		2008	Belgium	Shop	15	0.05	6.01	0.63	0.21	Van den Eede et al.,2011
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<0.11	4.3	-	<0,11	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<0.11	4	-	<0,11	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	0.12	162	-	5.6	Luongo and Östman.,2016
		2010	Roumania (Lasi)	Homes	47	<0.02	0.38	0.07	0.05	Dirtu et al.,2012
		2011–2012	Germany	Cars	12	<0.03	0.63	0.11	0.02	Brommer et al.,2012
		2011–2012	Germany	Offices	10	<0.03	0.41	0.22	-	Brommer et al.,2012
		2011–2012	Portugal	Homes	28	<0.00044	0.55	0.07	0.03	Coelho et al.,2016
		2011–2012	Germany	Daycare centers	63	<0.30	3.7	0.29	<0.30	Fromme et al.,2014
		2011–2012	Germany	Cars	19	<0.03	0.63	-	<0.03	Harrad et al.,2016
		2011–2012	Germany	Homes (living rooms)	22	<0.03	0.25	-	<0.03	Harrad et al.,2016
		2011–2012	Germany	Offices	25	<0.03	0.76	-	0.17	Harrad et al.,2016
		2011–2012	UK (West Midlands)	Cars	21	<0.03	1.2	0.14	<0.03	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Classroom	28	<0.03	0.46	0.17	0.12	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Homes (living room)	32	<0.03	0.09	0.04	<0.03	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Offices	61	<0.03	1.3	0.1	<0.03	Brommer and Harrad.,2015
		2012	Norway	Homes	48	-	0.98	0.12	0.06	Cequier et al.,2014
		2013	Czech Republic	Homes	30	0.01	0.16	-	0.05	Vykoukalová et al.,2017
		2013	UK	Homes	10	0.21	0.48	0.31	0.26	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	0.23	3.12	0.71	0.49	Kademoglou et al.,2017
		2013–2014	Norway (Oslo)	Homes (floor)	61	<0.190	2.95	-	<0.190	Xu et al.,2016

		2013–2014	Norway (Oslo)	Homes (surface)	61	<0.190	3.03	-	<0.190	Xu et al.,2016
		2015	Germany (Rhine/Main area)	Cars	11	0.21	1.3	0.62	0.41	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	<LOD	1.4	0.32	1.4	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	<LOD	1.2	0.38	0.28	Zhou et al.,2017
		-	Sweden (Stockolm)	Daycare center	10	0.1	6.2	2	1.2	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	N.D	1.7	0.6	0.3	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	N.D	3.2	0.7	0.2	Bergh et al.,2011
78-30-8	ToCP	2013	Czech Republic	Homes	30	N.D	0.25	-	0	Vykoukalová et al.,2017
78-32-0	TpCP	2013	Czech Republic	Homes	30	0	2.5	-	0.2	Vykoukalová et al.,2017
2528-38-3	TPEP	2010–2011	Portugal	Homes	28	<0.00028	0.03	0	0	Coelho et al.,2016
		2013	UK	Homes	10	18.33	1010	152.69	64.55	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	1	33.89	5.83	1.96	Kademoglou et al.,2017
115-86-6	TPHP	2008	Belgium	Homes (floor)	33	0.04	29.8	2.02	0.5	Van den Eede et al.,2011
		2008	Belgium	Shop	15	0.15	34.2	4.7	1.97	Van den Eede et al.,2011
		2008	Danmark (Odense)	Daycare centers (shelves,ledges,windows sills)	151	<0.94	210	-	2	Langer et al.,2016
		2008	Danmark (Odense)	Homes (children bedroom's,shelves,ledges,windows sills)	497	<0.94	91	-	<0.94	Langer et al.,2016
		2008	Swenden (Stockolm)	Homes	62	0.68	38	-	4.3	Luongo and Östman.,2016
		2010	Roumania (Lasi)	Homes	47	<0.02	22.6	1.6	0.5	Dirtu et al.,2012
		2010	Roumania (Lasi)	Homes	47	<0.01	0.04	<0.01	<0.01	Dirtu et al.,2012
		2010–2011	Germany		10	0.47	4.8	2.5	-	Brommer et al.,2012
		2010–2011	Germany	Cars	12	0.5	11	3	2.3	Brommer et al.,2012
		2010–2011	Portugal	Homes	28	0.11	5.2	1	0.66	Coelho et al.,2016
		2011–2012	Germany	Daycare centers	63	<0.30	64.5	2.56	0.5	Fromme et al.,2014
		2011–2012	Germany	Cars	19	0.33	11	-	1.8	Harrad et al.,2016
		2011–2012	Germany	Homes (living rooms)	22	0.07	18	-	0.23	Harrad et al.,2016
		2011–2012	Germany	Offices	25	0.2	8.8	-	1.5	Harrad et al.,2016
		2011–2012	UK (West Midlands)	Cars	21	0.27	170	15	3.3	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Classroom	28	0.22	90	12	4.1	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Homes (living room)	32	0.49	110	10	3.3	Brommer and Harrad.,2015
		2011–2012	UK (West Midlands)	Offices	61	0.56	50	8.2	4.3	Brommer and Harrad.,2015
		2012	Norway	Homes	48	1.21	4.85	1.24	0.98	Cequier et al.,2014
		2013	UK	Homes	10	0.19	9.55	2.74	1.51	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	0.2	2.92	0.93	0.83	Kademoglou et al.,2017
		2013–2014	Norway (Oslo)	Homes (floor)	61	0.16	276	-	0.72	Xu et al.,2016
		2013–2014	Norway (Oslo)	Homes (surface)	61	0.33	956	-	1.23	Xu et al.,2016
		2013–2015	Netherlands	Homes (playroom)	50	0.19	9.86	-	0.55	Sugeng et al.2018
		2015	Germany (Rhine/Main area)	Cars	11	0.72	74	9.2	2.2	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Homes	15	0.48	23	3.6	1.2	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	0.77	9.2	3.3	2.9	Zhou et al.,2017
		2016	The netherlands	Homes (on top of electronics)	11	0.29	45.33	10.35	9.79	Björnsdotter et al., 2018
		2016	The netherlands	Homes and Offices	12	0.17	12.85	3.07	1.44	Björnsdotter et al., 2018
		2017	Spain	Cars	15	0.76	142.46	18.31	4.44	Björnsdotter et al., 2018
		2017	Spain	Homes (on top of electronics)	13	1.27	2.62	59	2.42	Björnsdotter et al., 2018

		-	Greece	Cars	25	0.02	5.12	0.86	0.30 *	Christia et al.,2018
		-	Sweden (Stockolm)	Daycare center	10	0.3	17	3.5	1.9	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	0.1	4.2	1.6	1.2	Bergh et al.,2011
		-	Sweden (Stockolm)	Offices	10	0.9	32	8.8	5.3	Bergh et al.,2011
513-08-6	TPP	2008	Swenden (Stockolm)	Homes	62	<0.01	1.6	-	<0.01	Luongo and Östman.,2016
		2010–2011	Portugal	Homes	28	<0.86	10	3	2.4	Coelho et al.,2016
		2013	UK	Homes	10	<0.03	<0.03	<0.03	<0.03	Kademoglou et al.,2017
		2013–2014	Norway	Homes	10	<0.03	<0.03	<0.03	<0.03	Kademoglou et al.,2017
25653-16-1	TXP	2013	UK	Homes	10	<0.0011	0.54	0.08	0.03	Kademoglou et al.,2017
		2013	Czech Republic	Homes	30	N.D	N.D	-	N.D	Vykoukalová et al.,2017
		2013–2014	Norway	Homes	10	0	0.11	0.03	0.01	Kademoglou et al.,2017

-: information not available; N.D.: not detected; *: median calculated with detected measures LOD : limit of detection.

Supplementary Table S3. Concentrations of OPFRs in indoor air (ng/m3), Europe, 2000-2018.

CAS Number	Abbreviation	Period	Country	Sampling Location	Sample Size	Min	Max	Mean	Median	References
1241-94-7	EHDPP	2006–2007	Sweden (Stockolm)	Homes	169	N.D	24	5.6	<5.5	Bergh C et al.,2011
		2008	Sweden (Stockolm)	Homes	62	N.D	3.9	-	N.D	Luongo and Östman.,2016
		2012	Norway	Homes	47	-	3.51	0.489	0.119	Cequier et al.,2014
		2013	Czech Republic	Homes	29	0.193	1.09	-	0.375	Vykoukalová et al.,2017
		-	Sweden (Stockolm)	Homes	10	N.D	DET	N.D	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Day care center	10	N.D	2.2	0.4	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	N.D	14	1.8	N.D	Bergh et al.,2011
		2013–2014	Norway (Oslo)	Homes	61	<0.6	8	-	<0.6	Xu et al., 2016
		2014–2015	Sweden (Stockolm)	Office	23	<0.04	12	3.8	3.6	Wong et al., 2018
78-51-3	TBOEP	2006–2007	Sweden (Stockolm)	Homes	169	N.D	86	<31	<31	Bergh C et al.,2011
		2008	Sweden (Stockolm)	Homes	62	N.D	10	-	N.D	Luongo and Östman.,2016
		2012	Norway	Homes	47	-	18.2	1.45	0.598	Cequier et al.,2014
		2015	Germany (Rhine/Main area)	Offices	11	<0.68	5.33	0.79	<0.68	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	School	12	<0.68	17.51	1.77	<0.68	Zhou et al.,2017
78-33-1	TBPP	2013	Czech Republic	Homes	29	N.D	0.001	-	0.001	Vykoukalová et al.,2017
115-96-8	TCEP	2006–2007	Sweden (Stockolm)	Homes	169	N.D	230	10	4	Bergh C et al.,2011
		2008	Sweden (Stockolm)	Homes	62	N.D	223	-	3.9	Luongo and Östman.,2016
		2012	Norway	Homes	47	-	10.1	3.23	2.25	Cequier et al.,2014
		2013	Czech Republic	Homes	29	0.781	36.4	-	2.96	Vykoukalová et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	<0.75	5.69	1.01	0.56	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Schools	12	<0.75	4.65	0.52	<0.75	Zhou et al.,2017
		-	Sweden (Stockolm)	Homes	10	N.D	28	8.3	4.8	Bergh et al.,2011
		-	Sweden (Stockolm)	Day care center	10	7.8	230	47	25	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	N.D	140	21	10	Bergh et al.,2011
		2011–2012	Germany	Daycare centers	63	<2	33	2.2	<2	Fromme et al.,2014
		2013–2014	Norway (Oslo)	Homes	61	<0.9	76	-	3	Xu et al.,2016
		2014–2015	Sweden (Stockolm)	Office	23	6.7	20	11	10.9	Wong et al., 2018

		2015–2017	Sweden	Preschool	12	<2.2	<2.2	<2.2	<2.2	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<2.2	<2.2	<2.2	<2.2	Persson et al.2018
		2015–2017	Sweden	Preschool	12	<2.2	<2.2	<2.2	<2.2	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<2.2	<2.2	<2.2	<2.2	Persson et al.2018
13674-84-5	TCIPP	2006–2007	Sweden (Stockolm)	Homes	169	<0.5	1200	59	14	Bergh C et al.,2011
		2008	Sweden (Stockolm)	Homes	62	1.3	1179	-	19	Luongo and Östman.,2016
		2012	Norway	Homes	47	-	462	83.1	42.3	Cequier et al.,2014
		2013	Czech Republic	Homes	29	3.62	139	-	16.4	Vykoukalová et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	4.17	496.9	80.28	33.89	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Schools	12	4.14	68.83	17.53	9.99	Zhou et al.,2017
		-	Sweden (Stockolm)	Homes	10	2.4	64	15	5.6	Bergh et al.,2011
		-	Sweden (Stockolm)	Day care center	10	1.3	72	19	8.4	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	16	240	110	100	Bergh et al.,2011
		2011–2012	Germany	Daycare centers	63	<2	45	4.1	2.7	Fromme et al.,2014
		2013–2014	Norway (Oslo)	Homes	61	<1.2	987	-	128	Xu et al., 2017
		2014–2015	Sweden (Stockolm)	Office	23	85	1900	480	330	Wong et al., 2018
		2015–2017	Sweden	Preschool	12	<14	34	<14	<14	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<14	51	<14	<14	Persson et al.2018
		2015–2017	Sweden	Preschool	12	<14	93	21	<14	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<14	<14	<14	<14	Persson et al.2018
13674-87-8	TDCIPP	2012	Norway	Homes	47	-	10.6	0.394	0.084	Cequier et al.,2014
		2013	Czech Republic	Homes	29	0.228	0.572	-	0.311	Vykoukalová et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	<0.10	2.89	0.57	0.42	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	Schools	12	<0.10	29.86	2.99	<0.10	Zhou et al.,2017
		-	Sweden (Stockolm)	Homes	10	N.D	17	3.1	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Day care center	10	N.D	30	6.7	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	N.D	73	24	28	Bergh et al.,2011
		2014–2015	Sweden (Stockolm)	Office	23	N.D	-	N.D	-	Wong et al., 2018
		2015–2017	Sweden	Preschool	12	<11	<11	<11	<11	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<11	<11	<11	<11	Persson et al.2018
		2015–2017	Sweden	Preschool	12	<11	<11	<11	<11	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<11	<11	<11	<11	Persson et al.2018
78-42-2	TEHP	2013	Czech Republic	Homes	29	0.02	0.163	-	0.037	Vykoukalová et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	<0.06	0.87	0.16	<0.06	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	School	12	<0.06	17.51	1.77	<0.06	Zhou et al.,2017
		-	Sweden (Stockolm)	Homes	10	N.D	N.D	N.D	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Day care center	10	N.D	N.D	N.D	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	N.D	N.D	N.D	N.D	Bergh et al.,2011
		2013–2014	Norway (Oslo)	Homes	61	<4.6	42	-	<4.6	Xu et al., 2016
		2014–2015	Sweden (Stockolm)	Office	23	0.08	0.64	0.24	0.19	Wong et al., 2018
78-40-0	TEP	2006–2007	Sweden (Stockolm)	Homes	169	<0.18	300	14	4	Bergh C. et al.,2011
		2008	Sweden (Stockolm)	Homes	62	0.84	297	-	5.3	Luongo and Östman.,2016
		2015	Germany (Rhine/Main area)	Offices	11	<0.32	18.34	1.85	<0.32	Zhou et al.,2017

		2015	Germany (Rhine/Main area)	School	12	<0.32	27.13	2.5	<0.32	Zhou et al.,2017
		2015–2017	Sweden	Preschool	12	<17	<17	<17	<17	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<17	<17	<17	<17	Persson et al.2018
		2015–2017	Sweden	Preschool	12	<17	<17	<17	<17	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<17	25	<17	<17	Persson et al.2018
126-71-6	TIBP	2006–2007	Sweden (Stockolm)	Homes	169	2	54	11	9	Bergh C. et al.,2011
		2008	Sweden (Stockolm)	Homes	62	2.4	53	-	8.9	Luongo and Östman.,2016
		2015	Germany (Rhine/Main area)	Offices	11	0.77	22.37	6.65	5.65	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	School	12	1.59	36.78	12.76	8.56	Zhou et al.,2017
		-	Sweden (Stockolm)	Homes	10	3	66	18	13	Bergh et al.,2011
		-	Sweden (Stockolm)	Day care center	10	N.D	63	12	7.2	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	4.4	13	7.8	7.3	Bergh et al.,2011
64532-95-2	TiPPP	2013	Czech Republic	Homes	29	0.003	0.023	-	0.005	Vykoukalová et al.,2017
		2013–2014	Norway (Oslo)	Homes	61	<1.5	<1.5	-	<1.5	Xu et al., 2016
1330-78-5	TMPP	2012	Norway	Homes	47	<MLD	0.644	0.08	<MLD	Cequier et al.,2014
126-73-8	TNBP	2006-2007	Sweden (Stockolm)	Homes	169	2.5	370	20	11	Bergh C et al.,2011
		2008	Sweden (Stockolm)	Homes	62	2.5	94	-	13	Luongo and Östman.,2016
		2012	Norway	Homes	47	-	124	9.66	5.09	Cequier et al.,2014
		2013	Czech Republic	Homes	29	0.745	33.1	-	2.34	Vykoukalová et al.,2017
		2015	Germany (Rhine/Main area)	Offices	11	0.29	112.1	18.5	5.85	Zhou et al.,2017
		2015	Germany (Rhine/Main area)	School	12	<0.05	25.34	4.25	2.78	Zhou et al.,2017
		-	Sweden (Stockolm)	Homes	10	3.5	45	16	9.1	Bergh et al.,2011
		-	Sweden (Stockolm)	Day care center	10	3.7	320	61	18	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	N.D	100	21	2.3	Bergh et al.,2011
		2011–2012	Germany	Daycare centers	63	<2	1279	154	49	Fromme et al.,2014
		2011–2012	Germany	Daycare centers	63	<2	80	4	2.2	Fromme et al.,2014
		2013–2014	Norway (Oslo)	Homes	61	<2.7	119	-	14	Xu et al.,2016
		2014–2015	Sweden (Stockolm)	Office	23	0.92	2.1	1.2	1.2	Wong et al., 2018
		2014–2015	Sweden (Stockolm)	Office	23	0.9	4.3	1.8	1.3	Wong et al., 2018
		2015–2017	Sweden	Preschool	12	<19	<19	<19	<19	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<19	82	<19	<19	Persson et al.2018
		2015–2017	Sweden	Preschool	12	<19	21	<19	<19	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<19	150	36	<19	Persson et al.2018
115-86-6	TPHP	2006–2007	Sweden (Stockolm)	Homes	169	N.D	25	3.6	<3.1	Bergh C et al.,2011
		2008	Sweden	Homes	62	N.D	25	-	N.D	Luongo and Östman.,2016
		2012	Norway	Homes	47	-	1.65	0.375	0.258	Cequier et al.,2014
		2013	Czech Republic	Homes	29	0.304	0.91	-	0.592	Vykoukalová et al.,2017
		-	Sweden (Stockolm)	Day care center	10	N.D	0.9	0.1	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Homes	10	N.D	0.8	0.2	N.D	Bergh et al.,2011
		-	Sweden (Stockolm)	Office	10	N.D	2.7	0.6	N.D	Bergh et al.,2011
		2013–2014	Norway (Oslo)	Homes	61	<0.3	9	-	1	Xu et al., 2016
		2014–2015	Sweden (Stockolm)	Office	23	0.16	0.67	0.31	0.29	Wong et al., 2018
		2015–2017	Sweden	Preschool	12	<2.6	6.7	<2.6	<2.6	Persson et al.2018

513-08-6	TPP	2015–2017	Sweden	Preschool	16	<2.6	56	6.5	2.6	Persson et al.2018
		2015–2017	Sweden	Preschool	12	<2.6	4.8	<2.6	<2.6	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<2.6	33	8.2	3.5	Persson et al.2018
		2015	Germany(Rhine/Main area)	Offices	11	<0.16	0.64	0.16	<0.16	Zhou et al.,2017
		2015	Germany(Rhine/Main area)	School	12	-	-	<0.16	<0.16	Zhou et al.,2017
		2015–2017	Sweden	Preschool	12	<22	<22	<22	<22	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<22	30	<22	<22	Persson et al.2018
		2015–2017	Sweden	Preschool	12	<22	<22	<22	<22	Persson et al.2018
		2015–2017	Sweden	Preschool	16	<22	23	<22	<22	Persson et al.2018
		25653-16-1	TXP	2013	Czech Republic	Homes	29	N.D	N.D	-

-: information not available; N.D.: not detected; DET: detected; MLD: method limit detection.

Supplementary Table S4. Biological measurement of exposure, Europe, 2000 -2019.

Matrix	Metabolites	Name	Country	Population	Size	Sampling Year	Min	Max	Mean	Median	References
Urine (ng/ml)	BBOEP	TBOEP	Norway	Mother	42	-	<0.6	-	<0.6	<0.6	Cequier et al.,2014
	BBOEP	TBOEP	Norway	Children (6-12 years)	42	-	<0.6	-	<0.6	<0.6	Cequier et al.,2014
	BBOEP	TBOEP	Norway	Mother	244	2012	<0.18	0.29	<0.18	<0.18	Cequier et al.,2015
	BBOEP	TBOEP	Norway	Children (6-12 years)	112	2012	<0.18	1	0.19	<0.18	Cequier et al.,2015
	BBOEP	TBOEP	Belgium	Adult (23 men and 36 women)	59	-	-	7	-	-	Van den Eede et al.,2013
	BBOEP	TBOEP	Germany	Children (20-80 months)	54	2011–2012	-	-	0.36	0.16	Völkel et al., 2018
	BBOEHBP	TBOEP	Germany	Children (20-80 months)	54	2011–2012	-	-	0.33	0.6	Völkel et al., 2018
	DBEP	TBOEP	Germany	Children (22-80 months)	312	2011–2012	<0.015	24.9	3.2	2	Fromme et al.,2014
	BCEP	TCEP	Germany	General population (11-68 years)	30	2008	<0.1	27.5	-	<0.1	Schindler et al.,2009
	BCEP	TCEP	Belgium	Adult (23 men and 36 women)	59	-	-	9.5	-	-	Van den Eede et al.,2013
	DCEP	TCEP	Germany	Children (22-80 months)	312	2011–2012	<0.1	13.1	0.4	0.2	Fromme et al.,2014
	BCPP	TCIPP	Germany	General population (11-68 years)	25	2008	-	0.85	-	<0.25	Schindler et al.,2009
	BCPP	TCIPP	Belgium	Adult (23 men and 36 women)	59	-	-	6.2	-	-	Van den Eede et al.,2013
	DCPP	TCIPP	Germany	Children (22-80 months)	312	2011–2012	<0.2	8.4	0.2	<0.2	Fromme et al.,2014
	BDCIPP	TDCIPP	Norway	Mother	42	-	-	-	0.13 **	<0.4	Cequier et al.,2014
	BDCIPP	TDCIPP	Norway	Children (6-12 years)	42	-	-	-	0.2 **	-	Cequier et al.,2014
	BDCIPP	TDCIPP	Norway	Mother	244	2012	-	2	0.2	0.12	Cequier et al.,2015
	BDCIPP	TDCIPP	Norway	Children (6-12 years)	112	2012	-	3.7	0.33	0.23	Cequier et al.,2015
	BDCIPP	TDCIPP	Belgium	Adult (23 men and 36 women)	59	-	-	15	-	-	Van den Eede et al.,2013
	DEHP	TEHP	Germany	Men and women (14-85 years)	19	-	-	-	-	1.4	Reemtsma et al.,2011
	DEP	TEP	Germany	Men and women (14-85 years)	19	-	-	-	-	3.2	Reemtsma et al.,2011
	DmCP	TmCP	Germany	Children (22-80 months)	312	ND	N.D	N.D	N.D	N.D	Fromme et al.,2014
	DmCP	TmCP	Germany	General population (11-68 years)	30	2008	-	<0.5	-	<0.5	Schindler et al.,2009
	DBP	TNBP	Germany	General population (11-68 years)	25	2008	-	0.26	-	<0.25	Schindler et al.,2009
	DBP	TNBP	Belgium	Adult (23 men and 36 women)	59	-	-	3.5	-	-	Van den Eede et al.,2013
	DNBP	TNBP	Norway	Mother	42	-	<0.4	-	<0.4	<0.4	Cequier et al.,2014
	DNBP	TNBP	Norway	Children (6-12 years)	42	-	<0.4	-	<0.4	<0.4	Cequier et al.,2014
	DNBP	TNBP	Norway	Mother	244	2012	<0.12	0.49	<0.12	<0.12	Cequier et al.,2015
	DNBP	TNBP	Norway	Children (6-12 years)	112	2012	<0.12	0.87	<0.12	<0.12	Cequier et al.,2015
	DNBP	TNBP	Germany	Children (22-80 months)	312	2011–2012	<0.1	6.6	0.3	0.2	Fromme et al.,2014
	DoCP	ToCP	Germany	Children (22-80 months)	312	ND	N.D	N.D	N.D	N.D	Fromme et al.,2014
	DpCP	TpCP	Germany	Children (22-80 months)	312	ND	N.D	N.D	N.D	N.D	Fromme et al.,2014
	DpCP	TpCP	Germany	General population (11-68 years)	30	2008	-	<0.5	-	<0.5	Schindler et al.,2009

	DPHP	TPHP	Norway	Mother	42	-	-	-	1.1 **	-	Cequier et al.,2014
	DPHP	TPHP	Norway	Children (6-12 years)	42	-	-	-	0.57 **	-	Cequier et al.,2014
	DPHP	TPHP	Norway	Mother	244	2012	-	60	1.2	0.51	Cequier et al.,2015
	DPHP	TPHP	Norway	Children (6-12 years)	112	2012	-	135	3.2	1.1	Cequier et al.,2015
	DPHP	TPHP	Germany	Children (22-80 months)	312	2011–2012	<0.15	23.2	1.4	0.8	Fromme et al.,2014
	DPHP	TPHP	Sweden	Children (4 years)	113		0.45	35	-	1.8	Larsonn et al.,2014
	DPHP	TPHP	Germany	Men and women (14-85 years)	19	-	-	-	-	1.3	Reemtsma et al.,2011
	DPHP	TPHP	Belgium	Adult (23 men and 36 women)	59	-	-	13	-	-	Van den Eede et al.,2013
	DPP	TPHP	Germany	General population (11-68 years)	30	2008	-	5.47	-	0.52	Schindler et al.,2009
Hair (ng/g)	EHDPP		Norway	Mother	48	2012	5	265	-	27	Kucharska et al.,2015
	EHDPP		Norway	Children	54	2012	2	346	-	21	Kucharska et al.,2015
	TBOEP		Norway	Mother	48	2012	14	1253	-	65	Kucharska et al.,2015
	TBOEP		Norway	Children	54	2012	34	2411	-	318	Kucharska et al.,2015
	TCEP		Norway	Mother	48	2012	<33	163	-	72	Kucharska et al.,2015
	TCEP		Norway	Children	54	2012	<33	118	-	59	Kucharska et al.,2015
	TDCIPP		Norway	Mother	48	2012	<9	3744	-	30	Kucharska et al.,2015
	TDCIPP		Norway	Children	54	2012	<9	2698	-	31	Kucharska et al.,2015
	TMPP		Norway	Mother	48	2012	<2	134	-	8	Kucharska et al.,2015
	TMPP		Norway	Children	54	2012	<2	74	-	8	Kucharska et al.,2015
	TNBP		Norway	Mother	48	2012	5	672	-	22	Kucharska et al.,2015
	TNBP		Norway	Children	54	2012	3	150	-	11	Kucharska et al.,2015
	TPHP		Norway	Mother	48	2012	5	1256	-	52	Kucharska et al.,2015
	TPHP		Norway	Children	54	2012	6	363	-	63	Kucharska et al.,2015
	Milk (ng/g of lipid weight)	TBOEP		Spain	Breast milk	20	2015	<0.03	14.8	14.8	14.8
TCEP			Spain	Breast milk	20	2015	<0.02	-	-	-	Beser et al.,2019
TCIPP			Spain	Breast milk	20	2015	<0.13	12.5	12.5	12.5	Beser et al.,2019
TEP			Spain	Breast milk	20	2015	<0.02	7.8	4	3.4	Beser et al.,2019
TIPP			Spain	Breast milk	20	2015	<1.9	-	-	-	Beser et al.,2019
TMP			Spain	Breast milk	20	2015	<0.32	19	19	19	Beser et al.,2019
TNBP			Spain	Breast milk	20	2015	<0.03	10.9	10.9	10.9	Beser et al.,2019
TnPrP			Spain	Breast milk	20	2015	<1.9	-	-	-	Beser et al.,2019
TPHP			Spain	Breast milk	20	2015	<0.12	17.3	12.3	9.9	Beser et al.,2019
BdPhP			Sweden	Breast milk	286	1997–2007	N.D	-	-	N.D	Sundkvist et al.,2010
dBPhP			Sweden	Breast milk	286	1997–2007	N.D	-	-	N.D	Sundkvist et al.,2010
EHDPP			Sweden	Breast milk	286	1997–2007	3.5	13	-	-6.5	Sundkvist et al.,2010
TBOEP			Sweden	Breast milk	286	1997–2007	N.D	63	-	-4.7	Sundkvist et al.,2010
TCEP			Sweden	Breast milk	286	1997–2007	2.1	8.2	-	-4.9	Sundkvist et al.,2010
TCIPP			Sweden	Breast milk	286	1997–2007	22	82	-	-45	Sundkvist et al.,2010
TDCIPP			Sweden	Breast milk	286	1997–2007	1.6	5.6	-	-4.3	Sundkvist et al.,2010
TMPP			Sweden	Breast milk	286	1997–2007	N.D	3.7	-	-0.8	Sundkvist et al.,2010
TNBP			Sweden	Breast milk	286	1997–2007	3.5	13	-	-12	Sundkvist et al.,2010
ToCP		Sweden	Breast milk	286	1997–2007	N.D	-	-	N.D	Sundkvist et al.,2010	
TPHP		Sweden	Breast milk	286	1997–2007	3.2	11	-	-8.5	Sundkvist et al.,2010	

-: information no available; N.D.:not detected; **: mean calculatated with detected measures.

Annexe: Matériel supplémentaire de l'article « Pre- and post-natal exposure of children to organophosphate flame retardants: A nationwide survey in France »

Supplementary material

Table S1. Characteristics of study participants.

Determinants	Modalities	Mother-child pairs (N=259) N (%) or mean (SD)	Mothers population (N=388) N (%) or mean (SD)
Sex of child^b	Boy	106 (40.9)	208 (53.61)
	Girl	153 (59.1)	180 (46.39)
	NA (%)	3 (1.1)	0
Mother's age^{a b}	25-30	48 (18.5)	169 (43.56)
	31-35	100 (38.6)	135 (34.79)
	36-40	78 (30.1)	69 (17.78)
	>40	33 (12.7)	15 (3.87)
	NA (%)	2 (0.8)	0
Mother's BMI^b	18.5 - < 25	183 (70.7)	268 (69.07)
	<18.5	18 (6.9)	32 (8.25)
	25 - < 30	39 (15.1)	57 (14.69)
	30 or more	19 (7.3)	31 (7.99)
	NA (%)	2 (0.8)	4 (1)
Mother's education level^{a b}	<= BAC	61 (23.6)	103 (26.55)
	BAC +2	60 (23.1)	102 (26.29)
	> BAC	138 (53.3)	183 (47.16)
	NA (%)	2 (0.8)	3 (0.8)
Father's education level^{a b}	<= BAC	110 (42.5)	169 (43.56)
	BAC +2	54 (20.8)	79 (20.36)
	> BAC+2	95 (36.7)	140 (36.08)
	NA (%)	8 (3.1)	19 (5)
household income (euros)^{a b}	<=2999	59 (22.8)	130 (33.51)
	[3000 ; 3999]	71 (27.4)	121 (31.19)
	>= 4000	129 (49.8)	137 (35.31)
	NA (%)	12 (4.5)	21 (5.5)
Smoking status during pregnancy^b	Not a smoker	209 (80.7)	319 (82.22)
	Smoker	51 (19.3)	69 (17.78)
	NA (%)	2 (0.8)	3 (0.8)
Alcohol consumption during pregnancy^b	No	189 (72.9)	292 (75.26)
	Yes	70 (27.1)	96 (24.74)
	NA (%)	2 (0.8)	1 (0.3)
Renovation work^{a b}	No	178 (68.7)	172 (44.33)
	Yes	81 (31.3)	216 (55.67)
	NA (%)	2 (0.8)	4 (1)
Construction year of house^{a b}	> 2000	99 (38.2)	3 (0.8)
	[1970-2000]	69 (26.7)	5 (1.3)
	<1970	91 (35.1)	2 (0.1)
	NA (%)	52 (19.9)	373 (97.8)
Type of floor in the child's room^a	Tiles	24 (9.3)	x
	Lino	40 (15.4)	
	Carpet	14 (5.4)	
	Parquet	181 (69.9)	
	NA (%)	21 (8)	
BDE_47 (ng/g)^{a b}	<= 0.43	87 (33.2)	71 (18.30)
] 0.43 ; 1.23]	88 (33.6)	76 (19.59)
	>1.23	87 (33.2)	241 (62.11)
	NA (%)	0	0
BDE_209 (ng/g)^{a b}	<= 5.4	x	134 (34.54)
] 5.4 ; 11.8]		124 (31.96)
	>11.8		130 (33.51)
	NA (%)		0
Duration of breastfeeding (months)^a	<= 1	96 (37)	x
] 1 ; 4]	80 (30.9)	

	>4 NA (%)	83 (32.1) 2 (0.08)	
Time spent outdoors by children (hours/week) ^a	<= 4.5] 4.5 ; 7] >7 NA (%)	89 (33.9) 100 (38.3) 73 (27.8) 0	x
Time using electronic devices (hours/week) by children ^a	<= 2] 2 ; 4] >4 NA (%)	97 (37) 80 (30.5) 85 (32.5) 0	x
Number of windows in the child's room^a	1 2 NA (%)	220 (84.9) 39 (15.1) 2 (0.8)	x
Ventilation in the child's room^a	Yes No NA(%)	74 (28.6) 185 (71.4) 2 (0.8)	x
Season when hair was collected ^{ab}	Summer Autumn Winter Spring NA (%)	0 86 (33.2) 173 (66.8) 0 5 (1.9)	122 (31.44) 266 (68.56) 0 0 13 (3.4)
Number of people in the household^{ab}	<= 3 people 4 people >5 people NA (%)	63 (24.3) 126 (48.6) 70 (27.1) 2 (0.08)	172 (44.33) 145 (37.37) 71 (18.30) 13 (3.4)

N: number; SD: standard deviation; NA: missing data; ^a variables present in the 3.5-year questionnaire;

^b variables present in the maternity questionnaire or in the two-month questionnaire; x: data not collected in the maternity survey or in the two-month survey; the percentages of the modalities exclude NA.

Table S2. OPFR concentrations (ng/g) in mothers at birth (n=388) in 2011 and in children aged 3.5 years old (n=259) in 2014-2015.

OPFR	CAS number	Populations	Min	P25	P50	P75	P95	Max	Geometric mean (SD)
EHDPP	1241-94-7	Children	11	41	83	214	401	4423	97 (3)
		Mothers	1	22	35	56	101	51204	37 (3)
TBEP	78-51-3	Children	1	20	59	138	286	2082	53 (4)
		Mothers	31	34	35	50	137	2034	48 (2)
TBP	126-73-8	Children	5	15	19	27	34	89	20 (2)
		Mothers	10	27	35	45	54	84	34 (2)
TCEP	115-96-8	Children	1	9	14	24	47	623	14 (3)
		Mothers	1	6	12	23	52	939	13 (3)
TCPP	13674-84-5	Children	37	159	259	421	739	11848	269 (3)
		Mothers	14	189	256	374	669	3155	270 (2)
TDCPP	13674-87-8	Children	3	41	89	184	485	2343	94 (3)
		Mothers	2	25	49	109	252	16689	57 (4)
TEP	78-40-0	Children	2	9	13	18	29	153	13 (2)
		Mothers	4	23	49	76	97	238	42 (2)
TMCP	563-04-2	Children	1	1	3	8	20	1229	3 (5)
		Mothers	1	5	10	25	70	18194	12 (5)
TPP	115-86-6	Children	8	44	77	143	254	1874	82 (3)
		Mothers	5	37	63	106	298	8621	66 (3)

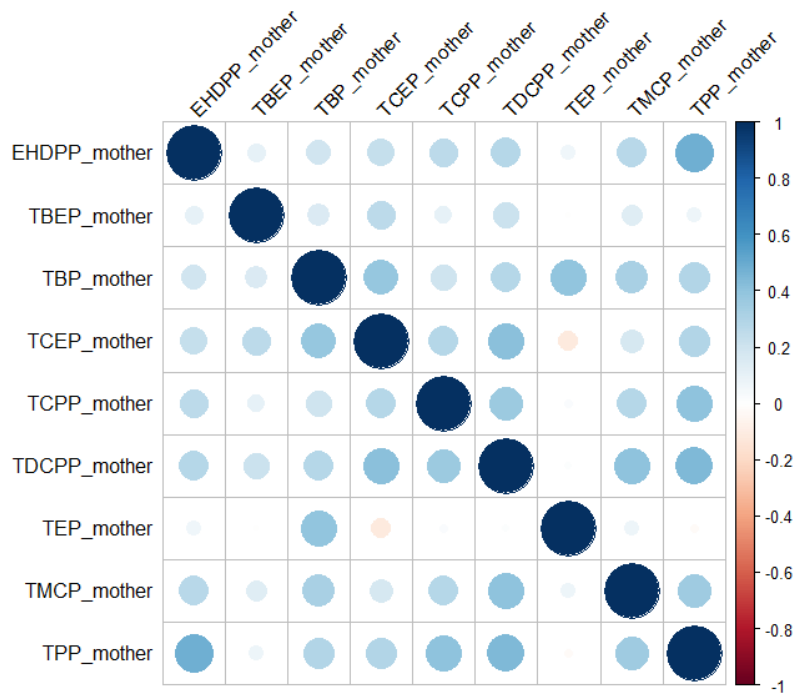


Fig S1. Weighted correlation matrix of OPFR concentrations among mothers (pre-natal exposures) in France (2011).

Associated p-values (fig S1)

	EHDP_mother	TBEP_mother	TBP_mother	TCEP_mother	TCPP_mother	TDCPP_mother	TEP_mother	TMCP_mother	TPP_mother
EHDP_mother	0.000000e+00	4.121104e-02	1.113760e-04	4.537312e-06	1.246941e-07	6.804621e-09	1.985643e-01	4.140708e-08	9.030634e-24
TBEP_mother	4.121104e-02	0.000000e+00	2.272421e-03	7.983381e-08	4.227894e-02	2.068323e-05	8.469163e-01	8.021370e-03	1.681794e-01
TBP_mother	1.113760e-04	2.272421e-03	0.000000e+00	1.624587e-15	3.687309e-05	1.889674e-08	2.660023e-16	9.943822e-11	2.869226e-09
TCEP_mother	4.537312e-06	7.983381e-08	1.624587e-15	0.000000e+00	1.123322e-08	1.019197e-17	1.975287e-02	3.899080e-04	2.547886e-09
TCPP_mother	1.246941e-07	4.227894e-02	3.687309e-05	1.123322e-08	0.000000e+00	2.063587e-13	6.073282e-01	6.064368e-09	9.669294e-17
TDCPP_mother	6.804621e-09	2.068323e-05	1.889674e-08	1.019197e-17	2.063587e-13	0.000000e+00	7.426285e-01	2.354499e-16	5.034561e-20
TEP_mother	1.985643e-01	8.469163e-01	2.660023e-16	1.975287e-02	6.073282e-01	7.426285e-01	0.000000e+00	1.623922e-01	6.213637e-01
TMCP_mother	4.140708e-08	8.021370e-03	9.943822e-11	3.899080e-04	6.064368e-09	2.354499e-16	1.623922e-01	0.000000e+00	4.342353e-13
TPP_mother	9.030634e-24	1.681794e-01	2.869226e-09	2.547886e-09	9.669294e-17	5.034561e-20	6.213637e-01	4.342353e-13	0.000000e+00

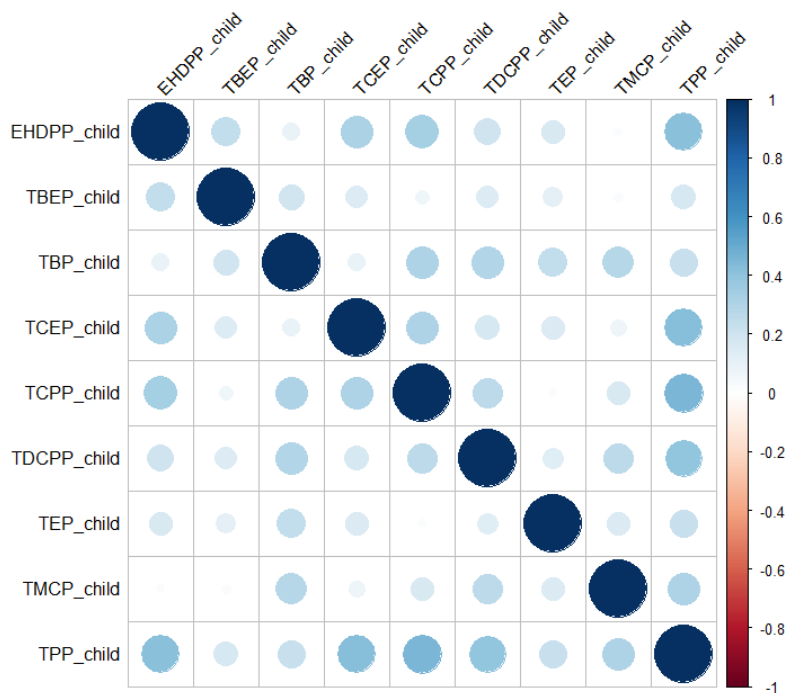


Fig S2. Weighted correlation matrix of OPFR concentrations among children (post-natal exposures) in France (2014-2015).

Associate p-values (fig S2)

	EHDP_child	TBEP_child	TBP_child	TCEP_child	TCPP_child	TDCPP_child	TEP_child	TMCP_child	TPP_child
EHDP_child	0.000000e+00	8.433249e-05	1.273648e-01	2.091489e-07	3.347701e-08	6.816099e-04	7.330937e-03	7.206524e-01	1.738184e-12
TBEP_child	8.433249e-05	0.000000e+00	1.933715e-03	2.153778e-02	2.977634e-01	1.689932e-02	5.942328e-02	6.588313e-01	4.911019e-03
TBP_child	1.273648e-01	1.933715e-03	0.000000e+00	1.282066e-01	4.005990e-07	9.003359e-07	8.352188e-05	2.540133e-06	2.640320e-04
TCEP_child	2.091489e-07	2.153778e-02	1.282066e-01	0.000000e+00	7.229113e-07	5.641546e-03	1.062510e-02	2.034261e-01	1.400405e-12
TCPP_child	3.347701e-08	2.977634e-01	4.005990e-07	7.229113e-07	0.000000e+00	1.097558e-05	6.840416e-01	9.102207e-03	2.148113e-14
TDCPP_child	6.816099e-04	1.689932e-02	9.003359e-07	5.641546e-03	1.097558e-05	0.000000e+00	2.793843e-02	1.961513e-05	3.532309e-11
TEP_child	7.330937e-03	5.942328e-02	8.352188e-05	1.062510e-02	6.840416e-01	2.793843e-02	0.000000e+00	1.034887e-02	1.939493e-04
TMCP_child	7.206524e-01	6.588313e-01	2.540133e-06	2.034261e-01	9.102207e-03	1.961513e-05	1.034887e-02	0.000000e+00	8.333390e-07
TPP_child	1.738184e-12	4.911019e-03	2.640320e-04	1.400405e-12	2.148113e-14	3.532309e-11	1.939493e-04	8.333390e-07	0.000000e+00

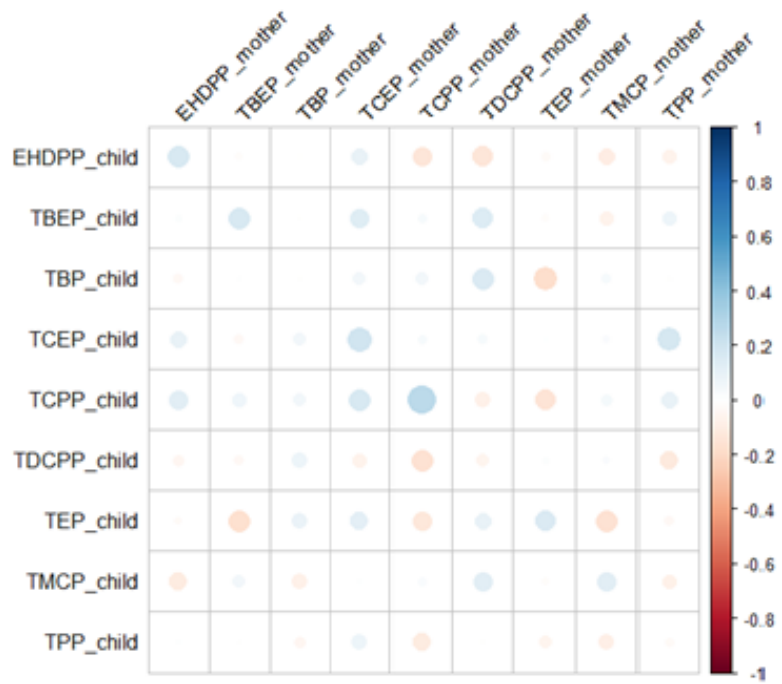


Fig S3. Weighted correlation matrix of OPFR concentrations among mother-child pairs in France.

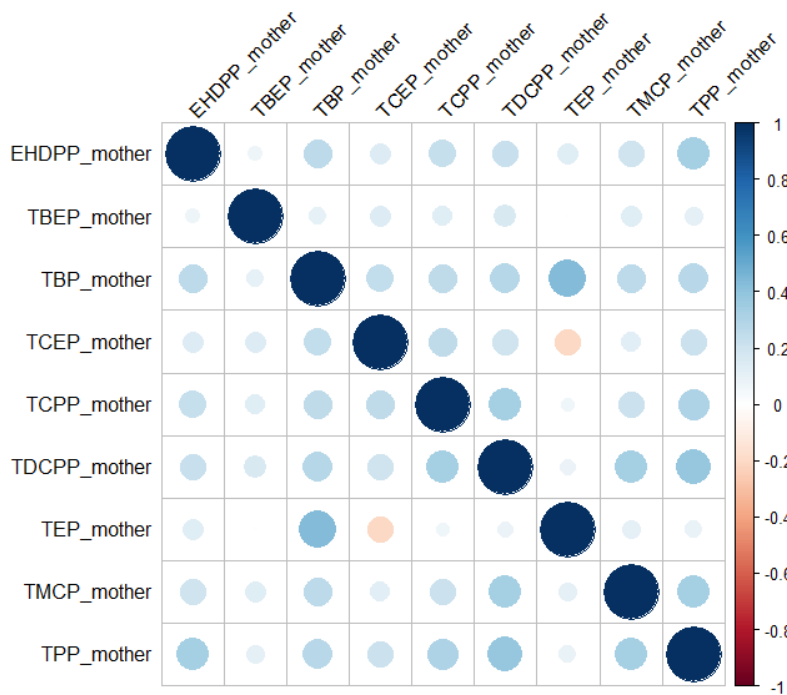


Fig S4. Unweighted correlation matrix of OPFR concentrations among mothers (n=388) in France (2011).

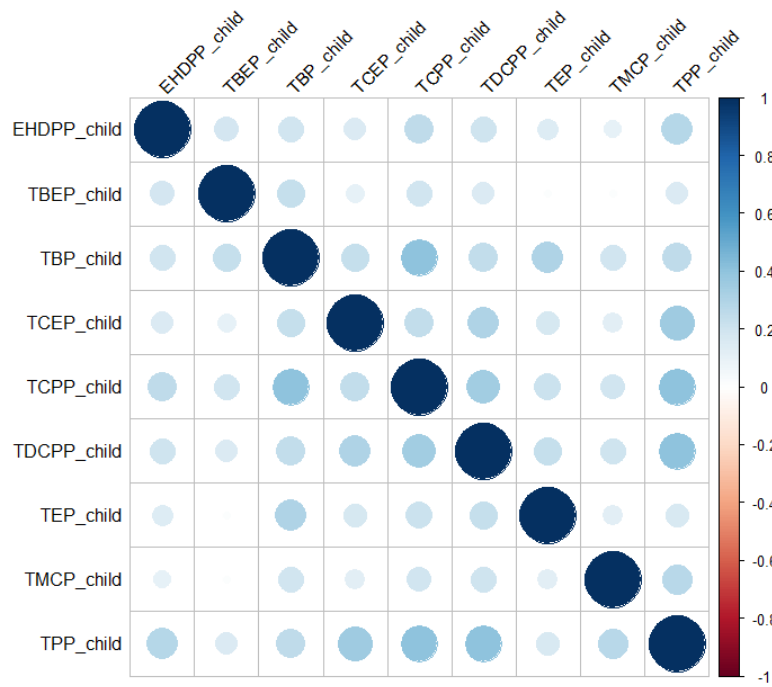


Fig S5. Unweighted correlation matrix of OPFR concentrations among children (n=259) in France (2014-2015).

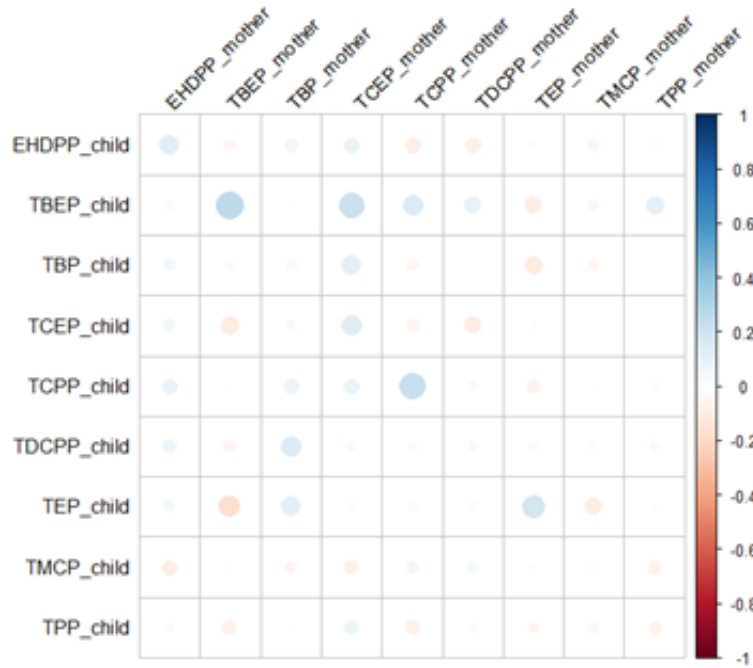


Fig S6. Unweighted correlation matrix of OPFR concentrations among mother-child pairs in France (n=259).

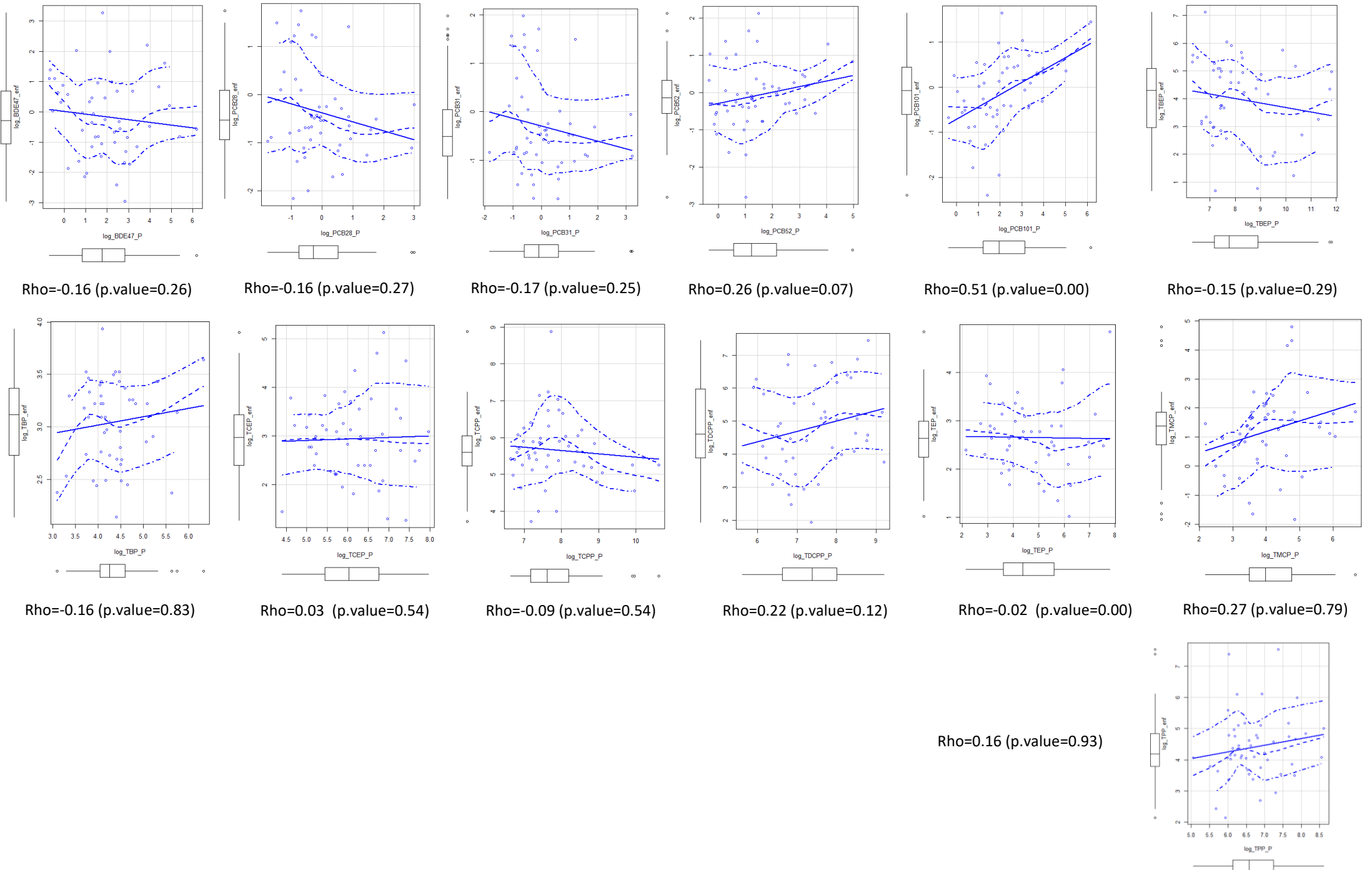


Fig S7. Correlation between OPFR concentration in children and OPFR concentration measured in dust for each OPFR substance with detection rate > 20 %.

Table S3. Association between OPFR concentrations and potential determinants among mothers at birth in France (2011).

OPFR determinants	EHDPP		TBEP		TBP		TCEP		TCPP		TDCPP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P
Sources												
Home renovation work before birth												
No	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	0.08 [0.09 ; 0.26]	0.35	0.07 [-0.08 ; 0.21]	0.35	0.08 [0.00 ; 0.16]	0.04	0.37 [0.13 ; 0.13]	<0.01	0.15 [0.01 ; 0.29]	0.03	0.53 [0.26 ; 0.79]	<0.01
Mothers' BDE 47 concentration at birth (ng/g)												
<= 0.43	Ref		Ref		Ref		Ref		Ref		Ref	
] 0.43 ; 1.23]	0.01 [-0.31 ; 0.34]	0.93	0.12 [-0.14 ; 0.38]	0.38	0.17 [0.03 ; 0.30]	0.01	0.03 [-0.40 ; 0.47]	0.87	0.04 [-0.21 ; 0.29]	0.74	0.04 [-0.44 ; 0.53]	0.87
>1.23	0.23 [-0.02 ; 0.48]	0.07	0.11 [-0.09 ; 0.31]	0.29	0.18 [0.08 ; 0.29]	<0.01	0.42 [0.09 ; 0.76]	0.01	0.43 [0.24 ; 0.62]	<0.01	0.16 [-0.21 ; 0.54]	0.39
Mothers' BDE 209 concentration at birth (ng/g)												
<= 5.4	Ref		Ref		Ref		Ref		Ref		Ref	
] 5.4 ; 11.8]	0.02 [-0.20 ; 0.24]	0.85	0.08 [-0.09 ; 0.26]	0.35	0.03 [-0.06 ; 0.12]	0.50	0.17 [-0.14 ; 0.47]	0.29	0.05 [-0.13 ; 0.22]	0.60	0.72 [0.42 ; 1.02]	<0.01
>11.8	0.39 [0.18 ; 0.60]	<0.01	0.31 [0.14 ; 0.48]	<0.01	0.10 [0.01 ; 0.19]	0.03	0.38 [0.08 ; 0.67]	0.01	0.15 [-0.02 ; 0.32]	0.09	1.49 [1.21 ; 1.78]	<0.01
Socio-demographic												
Mother's level of education at birth												
<= BAC	Ref		Ref		Ref		Ref		Ref		Ref	
BAC +2	-0.28 [-0.52 ; -0.03]	0.02	0.03 [-0.17 ; 0.23]	0.75	-0.08 [-0.19 ; 0.02]	0.11	-0.19 [-0.52 ; 0.15]	0.27	0.19 [-0.00 ; 0.38]	0.054	0.01 [-0.35 ; 0.38]	0.92
> BAC +2	-0.27 [-0.47 ; -0.07]	<0.01	0.11 [-0.05 ; 0.28]	0.16	-0.04 [-0.13 ; 0.05]	0.38	-0.15 [-0.42 ; 0.12]	0.28	0.19 [0.03 ; 0.35]	0.02	-0.13 [-0.43 ; 0.17]	0.39
Household income at birth (euros)												
<=2999	Ref		Ref		Ref		Ref		Ref		Ref	
[3000 ; 3999]	-0.05 [-0.27 ; 0.17]	0.67	0.02 [-0.16 ; 0.20]	0.84	-0.04 [-0.13 ; 0.06]	0.46	-0.35 [-0.65 ; -0.05]	0.02	0.03 [-0.15 ; 0.21]	0.74	-0.08 [-0.42 ; 0.26]	0.64
> 4000	-0.40 [-0.60 ; -0.17]	0.01	0.11 [0.06 ; 0.29]	0.21	-0.06 [-0.15 ; 0.03]	0.22	0.11 [-0.19 ; 0.40]	0.48	-0.04 [-0.22 ; 0.13]	0.62	0.02 [-0.31 ; 0.35]	0.92
Number of people in the household at birth												
<=3 persons	Ref		Ref		Ref		Ref		Ref		Ref	
4 persons	0.22 [0.02 ; 0.42]	0.03	0.14 [-0.02 ; 0.30]	0.08	-0.06 [-0.14 ; 0.02]	0.16	-0.05 [-0.32 ; 0.22]	0.72	-0.13 [-0.29 ; 0.03]	0.10	-0.20 [-0.40 ; 0.20]	0.53
>5 persons	0.27 [0.03 ; 0.52]	0.03	0.20 [0.001 ; 0.40]	0.048	-0.19 [-0.29 ; -0.08]	<0.01	-0.32 [-0.66 ; -0.01]	0.06	-0.09 [-0.29 ; 0.10]	0.37	0.07 [-0.30 ; 0.45]	0.70

Table S3. Association between OPFR concentrations and potential determinants among mothers at birth in France (2011).

Pre-pregnancy BMI												
18.5 - < 25	Ref		Ref		Ref		Ref		Ref		Ref	
<18.5	-0.40 [-0.72; -0.09]	0.01	0.00 [-0.25 ; 0.27]	0.95	0.12 [-0.01 ; 0.25]	0.07	-0.72 [-1.14 ; -0.29]	<0.01	-0.36 [-0.61 ; -0.11]	<0.01	-0.81 [-1.27 ; -0.35]	<0.01
25 - < 30	-0.13 [-0.40 ; 0.14]	0.36	-0.19 [-0.41 ; 0.03]	0.10	0.09 [-0.02 ; 0.21]	0.09	-0.22 [-0.59 ; 0.14]	0.23	-0.22 [-0.44 ; -0.01]	0.04	-0.39 [-0.79 ; 0.01]	0.05
30 or more	0.29 [0.04 ; 0.53]	0.02	0.16 [-0.04 ; 0.37]	0.10	0.30 [0.20 ; 0.40]	<0.01	0.53 [0.20 ; 0.86]	<0.01	0.21 [0.01 ; 0.40]	0.04	0.62 [0.26 ; 0.98]	<0.01
Environmental												
Season of mothers' hair sampling												
Autumn	Ref		Ref		Ref		Ref		Ref		Ref	
Summer	0.41 [0.22 ; 0.60]	<0.01	0.21 [0.05 ; 0.40]	<0.01	0.02 [-0.06 ; 0.10]	0.56	0.25 [-0.01 ; 0.51]	0.06	0.00 [-0.15 ; 0.15]	0.99	-0.31 [-0.60 ; -0.02]	0.04

OPFR determinants	TEP		TMCP		TPP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P
Sources						
Home renovation work before birth						
No	Ref		Ref		Ref	
Yes	0.02 [-0.14 ; 0.19]	0.80	0.43 [0.09 ; 0.77]	0.01	0.43 [0.22 ; 0.65]	<0.01
Mothers' BDE 47 concentration at birth (ng/g)						
<= 0.43	Ref		Ref		Ref	
] 0.43 ; 1.23]	0.03 [-0.30 ; 0.32]	0.85	0.99 [0.39 ; 1.59]	<0.01	-0.10 [-0.50 ; 0.29]	0.60
>1.23	0.30 [0.04 ; 0.50]	0.02	1.26 [0.80 ; 1.72]	<0.01	0.32 [-0.02 ; 0.63]	0.04
Mothers' BDE 209 concentration at birth (ng/g)						
<= 5.4	Ref		Ref		Ref	
] 5.4 ; 11.8]	-0.14 [-0.35 ; 0.06]	0.16	0.86 [0.45 ; 1.27]	<0.01	0.27 [0.00 ; 0.53]	0.04
>11.8	0.10 [-0.09 ; 0.30]	0.30	1.11 [0.72 ; 1.51]	<0.01	0.66 [0.41 ; 0.92]	<0.01
Socio-demographic						
Mother's level of education at birth						
<= BAC	Ref		Ref		Ref	
BAC +2	0.03 [-0.19 ; 0.26]	0.77	0.31 [-0.15 ; 0.78]	0.19	-0.16 [-0.46 ; 0.15]	0.32
> BAC + 2	0.08 [-0.10 ; 0.26]	0.39	0.24 [-0.63 ; 0.14]	0.21	-0.04 [-0.29 ; 0.21]	0.77
Household income at birth (euros)						
<=2999	Ref		Ref		Ref	
[3000 ; 3999]	-0.17 [-0.37 ; 0.04]	0.11	0.00 [-0.42 ; 0.43]	0.97	-0.11 [-0.42 ; 0.18]	0.44
> 4000	-0.36 [-0.56 ; -0.16]	<0.01	-0.64 [-1.05 ; -0.22]	<0.01	-0.00 [-0.25 ; -0.24]	0.96
Number of people in the household at birth						
<=3 persons	Ref		Ref		Ref	
4 persons	-0.06 [-0.24 ; 0.12]	0.63	0.16 [-0.22 ; 0.54]	0.41	-0.04 [-0.28 ; 0.20]	0.75
>5 persons	-0.08-10 ⁻⁵ [-0.23 ; 0.23]	0.86	-0.13 [-0.61 ; 0.34]	0.58	-0.29 [-0.59 ; 0.02]	0.06
Pre-pregnancy BMI						
18.5 - < 25	Ref		Ref		Ref	
<18.5	0.43 [-0.14 ; -0.72]	<0.01	-0.10 [-0.71 ; 0.50]	0.73	-0.39 [0.77 ; -0.01]	0.04
25 - < 30	0.22 [-0.03 ; 0.48]	0.08	-0.04 [-0.56 ; 0.48]	0.87	-0.35 [-0.68 ; -0.02]	0.04

Table S3. Association between OPFR concentrations and potential determinants among mothers at birth in France (2011).

30 or more	0.24 [0.01 ; 0.47]	0.04	0.88 [0.41 ; 1.35]	<0.01	0.57 [0.28 ; 0.87]	<0.01
Environmental						
Season of mothers' hair sampling	Ref		Ref		Ref	
Autumn	-0.19 [-0.36 ; 0.01]	0.04	-0.44 [-0.80 ; -0.07]	0.02	0.07 [-0.16 ; 0.31]	0.55
Summer						

Table S4. Association between OPFR concentrations and potential determinants among children in France (2014-2015).

OPFR determinants	EHDPP		TBEP		TBP		TCEP		TCPP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P
Sources										
Home renovation work at 3.5 years of child during the year before the survey										
No	Ref		Ref		Ref		Ref		Ref	
Yes	0.16 [-0.14 ; 0.46]	0.30	-0.20 [-0.53 ; 0.14]	0.24	0.04 [-0.07 ; 0.15]	0.44	-0.24 [-0.50 ; 0.03]	0.08	0.08 [-0.15 ; 0.30]	0.50
Residential home year construction at 3.5 years of child										
>2000	Ref		Ref		Ref		Ref		Ref	
[1970-2000]	0.06 [-0.28 ; 0.41]	0.72	0.12 [-0.26 ; 0.50]	0.54	0.05 [-0.07 ; 0.18]	0.40	-0.01 [-0.31 ; 0.29]	0.93	0.19 [-0.06 ; 0.45]	0.14
<1970	0.09 [-0.25 ; 0.43]	0.62	0.20 [-0.17 ; 0.57]	0.29	0.02 [-0.11 ; 0.14]	0.80	0.23 [-0.07 ; 0.52]	0.14	0.22 [-0.03 ; 0.47]	0.08
Type of floor in the child's room										
Tile	Ref		Ref		Ref		Ref		Ref	
Lino	0.12 [-0.42 ; 0.66]	0.66	0.71 [0.12 ; 1.31]	0.02	-0.05 [-0.25 ; 0.15]	0.62	0.16 [-0.32 ; 0.64]	0.51	0.24 [-0.17 ; 0.64]	0.25
Carpet	0.71 [-0.07 ; 1.49]	0.07	0.29 [-0.57 ; 1.14]	0.51	0.02 [-0.26 ; 0.31]	0.88	0.83 [0.15 ; 1.52]	0.02	0.08 [-0.50 ; 0.65]	0.79
Parquet	0.34 [-0.10 ; 0.78]	0.13	0.61 [0.13 ; 1.09]	0.01	-0.07 [-0.24 ; 0.09]	0.37	0.27 [-0.11 ; 0.66]	0.16	0.34 [0.01 ; 0.66]	0.04
Duration of breastfeeding (months)										
<= 1	Ref		Ref		Ref		Ref		Ref	
] 1 ; 4]	-0.04 [-0.38 ; 0.31]	0.84	0.05 [-0.33 ; 0.43]	0.80	-0.05 [-0.18 ; 0.08]	0.44	-0.24 [-0.54 ; 0.07]	0.13	-0.20 [-0.46 ; 0.06]	0.13
>4	0.07 [-0.27 ; 0.40]	0.69	0.33 [-0.04 ; 0.70]	0.08	-0.03 [-0.15 ; 0.09]	0.61	-0.07 [-0.37 ; 0.22]	0.64	-0.04 [-0.28 ; 0.21]	0.77
Children's BDE 47 concentration at 3.5 years(ng/g)										
<= 0.43	Ref		Ref		Ref		Ref		Ref	
] 0.43 ; 1.23]	0.20 [-0.15 ; 0.55]	0.26	-0.13 [-0.52 ; 0.26]	0.51	0.02 [-0.11 ; 0.15]	0.77	-0.12 [-0.43 ; 0.19]	0.45	0.22 [-0.04 ; 0.47]	0.09
>1.23	0.36 [0.03 ; 0.70]	0.03	-0.20 [-0.58 ; 0.17]	0.29	0.13 [0.01 ; 0.26]	0.03	-0.08 [-0.38 ; 0.22]	0.58	0.46 [0.22 ; 0.71]	<0.01
Socio-demographic										
Mother's education level at 3.5 years of child										
<= BAC	Ref		Ref		Ref		Ref		Ref	
BAC +2	0.29 [-0.11 ; 0.70]	0.15	0.08 [-0.37 ; 0.53]	0.72	0.01 [-0.14 ; 0.15]	0.87	-0.31 [-0.66 ; 0.05]	0.09	0.13 [-0.17 ; 0.53]	0.41
> BAC	0.03 [-0.29 ; 0.34]	0.88	0.10 [-0.26 ; 0.45]	0.59	-0.08 [-0.20 ; 0.04]	0.18	-0.20 [-0.48 ; 0.08]	0.16	-0.01 [-0.24 ; 0.23]	0.98
Household income at 3.5 years of child (euros)										
<=2999	Ref		Ref		Ref		Ref		Ref	
[3000 ; 3999]	-0.19 [-0.56 ; 0.18]	0.31	-0.04 [-0.44 ; 0.37]	0.86	-0.22 [-0.36 ; -0.09]	<0.01	-0.06 [-0.38 ; 0.27]	0.73	-0.05 [-0.32 ; 0.23]	0.75
> 4000	-0.11 [-0.45 ; 0.23]	0.54	0.01 [-0.37 ; 0.38]	0.99	-0.20 [-0.32 ; -0.09]	<0.01	-0.14 [-0.44 ; 0.15]	0.34	-0.13 [-0.38 ; 0.12]	0.31
Number of persons in the household at 3.5 years of child										
<= 3 persons	Ref		Ref		Ref		Ref		Ref	
4 persons	-0.17 [-0.53 ; 0.18]	0.34	-0.09 [-0.48 ; 0.31]	0.67	-0.11 [-0.24 ; 0.02]	0.11	0.11 [-0.20 ; 0.43]	0.47	-0.06 [-0.32 ; 0.20]	0.65
>5 persons	-0.02 [-0.41 ; 0.37]	0.91	0.16 [-0.27 ; 0.58]	0.47	-0.15 [-0.29 ; -0.01]	0.04	0.13 [-0.21 ; 0.48]	0.44	-0.13 [-0.42 ; 0.16]	0.38
Pre-pregnancy BMI										
18.5 - < 25	Ref		Ref		Ref		Ref		Ref	

Table S4. Association between OPFR concentrations and potential determinants among children in France (2014-2015).

<18.5	0.04 [-0.60 ; 0.68]	0.90	-1.41 [-2.13 ; -0.70]	<0.01	0.22 [-0.01 ; 0.46]	0.06	-0.71 [-1.32 ; -0.11]	0.02	0.23 [-0.27 ; 0.73]	0.37
25 - < 30	0.35 [-0.75 ; 0.05]	0.10	-0.40 [-0.85 ; 0.05]	0.08	0.11 [-0.26 ; 0.04]	0.14	-0.24 [-0.62 ; 0.14]	0.21	-0.24 [-0.56 ; 0.07]	0.13
30 ou plus	-0.00 [-0.39 ; 0.38]	0.98	-0.74 [-1.17 ; -0.31]	<0.01	0.07 [-0.08 ; 0.21]	0.36	-0.17 [-0.54 ; -0.54]	0.35	0.05 [-0.25 ; 0.35]	0.73
Behavioural										
Time spent outdoors by children at age 3.5 years (hours/week)										
<= 4.5 hours	Ref		Ref		Ref		Ref		Ref	
] 4.5 ; 7] hours	0.29 [-0.05 ; 0.64]	0.09	0.21 [-0.17 ; 0.58]	0.28	-0.10 [-0.23 ; 0.03]	0.11	0.29 [-0.01 ; 0.58]	0.06	0.13 [-0.12 ; 0.39]	0.30
>7hours	0.26 [-0.11 ; 0.62]	0.16	-0.19 [-0.59 ; 0.21]	0.36	-0.01 [-0.14 ; 0.13]	0.92	-0.07 [-0.39 ; 0.24]	0.65	0.12 [-0.15 ; 0.39]	0.39
Time spent using electronic devices by children at 3.5 years (hours/week)										
<= 2 hours	Ref		Ref		Ref		Ref		Ref	
] 2 ; 4] hours	-0.06 [-0.43 ; 0.31]	0.74	-0.45 [-0.85 ; -0.04]	0.03	-0.11 [-0.24 ; 0.03]	0.13	-0.45 [-0.77 ; -0.13]	<0.01	-0.11 [-0.38 ; 0.17]	0.45
>4 hours	-0.22 [-0.55 ; 0.11]	0.19	-0.15 [-0.52 ; 0.21]	0.41	-0.01 [-0.13 ; 0.11]	0.90	-0.06 [-0.35 ; 0.22]	0.66	-0.06 [-0.30 ; 0.19]	0.66
Number of windows in the child's room										
1	Ref		Ref		Ref		Ref		Ref	
2	-0.14 [-0.55 ; 0.26]	0.48	0.16 [-0.19 ; 0.51]	0.38	0.03 [-0.12 ; 0.18]	0.70	0.38 [0.03 ; 0.74]	0.03	0.01 [-0.29 ; 0.31]	0.93
Ventilation in the child's room										
Yes	Ref		Ref		Ref		Ref		Ref	
No	-0.16 [-0.48 ; 0.15]	0.31	-0.04 [-0.49 ; 0.41]	0.86	-0.02 [-0.13 ; 0.10]	0.80	-0.13 [-0.41 ; 0.15]	0.35	0.01 [-0.22 ; 0.24]	0.92
Environmental										
Season of children's hair sampling at 3.5 years										
Autumn	Ref		Ref		Ref		Ref		Ref	
Winter	-0.17 [-0.46 ; 0.12]	0.25	-0.23 [-0.55 ; 0.09]	0.16	-0.08 [-0.18 ; 0.03]	0.15	-0.15 [-0.41 ; 0.10]	0.25	-0.19 [-0.40 ; 0.02]	0.08

OPFR determinants	TDCPP		TEP		TMCP		TPP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]		β [IC95%]	P
Sources								
Home renovation work at 3.5 years of child during the year before the survey								
No	Ref		Ref		Ref		Ref	
Yes	-0.26 [-0.58 ; 0.05]	0.10	-0.11 [-0.29 ; 0.08]	0.27	0.19 [-0.23 ; 0.61]	0.38	0.02 [-0.22 ; 0.27]	0.85
Residential home year construction at 3.5 years of child								
>2000	Ref		Ref		Ref		Ref	
[1970-2000]	-0.01 [-0.37 ; 0.35]	0.97	-0.07 [-0.28 ; 0.14]	0.51	0.18 [-0.30 ; 0.66]	0.46	0.14 [-0.13 ; 0.42]	0.31
<1970	-0.02 [-0.38 ; 0.33]	0.90	0.15 [-0.06 ; 0.36]	0.16	0.46 [-0.01 ; 0.93]	0.06	0.22 [-0.05 ; 0.50]	0.11
Type of floor in the child's room								
Tile	Ref		Ref		Ref		Ref	
Lino	0.11 [-0.46 ; 0.68]	0.71	0.29 [-0.04 ; 0.63]	0.08	0.58 [-0.18 ; 1.35]	0.14	0.59 [0.15 ; 1.03]	<0.01
Carpet	0.15 [-0.67 ; 0.96]	0.73	-0.17 [-0.65 ; 0.31]	0.48	0.41 [-0.69 ; 1.50]	0.46	0.57 [-0.05 ; 1.20]	0.07
Parquet	0.21 [-0.26 ; 0.67]	0.38	0.12 [-0.15 ; 0.39]	0.37	0.30 [-0.31 ; 0.92]	0.33	0.36 [0.01 ; 0.71]	0.05
Duration of breastfeeding (months)								
<= 1	Ref		Ref		Ref		Ref	

Table S4. Association between OPFR concentrations and potential determinants among children in France (2014-2015).

] 1 ; 4] >4	-0.03 [-0.40 ; 0.33] -0.16 [-0.51 ; 0.19]	0.86 0.38	-0.19 [-0.40 ; 0.03] -0.26 [-0.47 ; -0.06]	0.09 0.01	-0.45 [-0.94 ; 0.03] -0.01 [-0.47 ; 0.46]	0.07 0.98	-0.13 [-0.42 ; 0.15] -0.02 [-0.29 ; 0.25]	0.35 0.89
Children's BDE 47 concentration at 3.5 years (ng/g)								
<= 0.43	Ref		Ref		Ref		Ref	
] 0.43 ; 1.23]	0.20 [-0.17 ; 0.57]	0.28	0.12 [-0.09 ; 0.34]	0.26	0.04 [-0.46 ; 0.53]	0.89	0.30 [0.02 ; 0.58]	0.03
>1.23	0.29 [-0.06 ; 0.65]	0.11	0.15 [-0.06 ; 0.36]	0.17	0.18 [-0.29 ; 0.66]	0.45	0.24 [-0.04 ; 0.51]	0.08
Socio-demographic								
Mother's education level at 3.5 years of child								
<= BAC	Ref		Ref		Ref		Ref	
BAC +2	-0.06 [-0.47 ; 0.36]	0.79	0.02 [-0.23 ; 0.27]	0.86	0.45 [-0.12 ; 1.01]	0.12	0.18 [-0.15 ; 0.51]	0.28
> BAC	-0.43 [-0.76 ; -0.10]	0.01	-0.21 [-0.40 ; -0.01]	0.04	0.17 [-0.28 ; 0.61]	0.47	0.17 [-0.09 ; 0.43]	0.19
Household income at 3.5 years of child (euros)								
<=2999	Ref		Ref		Ref		Ref	
]3000 ; 3999]	-0.47 [-0.85 ; -0.09]	0.01	-0.41 [-0.63 ; -0.19]	<0.01	-0.37 [-0.88 ; 0.15]	0.16	-0.17 [-0.47 ; 0.13]	0.26
> 4000	-0.49 [-0.84 ; -0.14]	<0.01	-0.34 [-0.54 ; -0.13]	<0.01	-0.24 [-0.72 ; 0.23]	0.32	-0.09 [-0.37 ; 0.18]	0.51
Number of persons in the household at 3.5 years of child								
<= 3 persons	Ref		Ref		Ref		Ref	
4 persons	-0.13 [-0.50 ; 0.24]	0.48	-0.04 [-0.26 ; 0.17]	0.69	-0.45 [-0.94 ; 0.04]	0.07	-0.02 [-0.31 ; 0.26]	0.87
>5 persons	0.27 [-0.13 ; 0.67]	0.19	-0.06 [-0.30 ; 0.18]	0.63	-0.66 [-1.19 ; -0.12]	0.02	0.01 [-0.30 ; 0.33]	0.94
Pre-pregnancy BMI								
18.5 - < 25	Ref		Ref		Ref		Ref	
<18.5	0.26 [-0.47 ; 1.00]	0.48	-0.12 [-0.56 ; 0.31]	0.57	-0.54 [-1.44 ; 0.37]	0.24	0.28 [-0.31 ; 0.75]	0.42
25 - < 30	-0.23 [-0.69 ; 0.23]	0.33	0.14 [-0.13 ; 0.42]	0.29	-0.52 [-1.09 ; 0.05]	0.07	0.18 [-0.52 ; 0.15]	0.28
30 ou plus	-0.01 [-0.46 ; 0.43]	0.95	-0.08 [-0.34 ; 0.18]	0.53	-0.39 [-0.93 ; 0.15]	0.16	-0.19 [-0.51 ; -0.13]	0.24
Behavioural								
Time spent outdoors by children at 3.5 years (hours/week)								
<= 4.5 hours	Ref		Ref		Ref		Ref	
] 4.5 ; 7] hours	0.54 [0.19 ; 0.90]	<0.01	-0.06 [-0.27 ; 0.15]	0.58	0.26 [-0.21 ; 0.74]	0.28	0.26 [-0.02 ; 0.53]	0.07
>7hours	0.43 [0.06 ; 0.81]	0.02	-0.20 [-0.42 ; 0.02]	0.08	-0.24 [-0.74 ; 0.27]	0.35	-0.07 [-0.37 ; 0.22]	0.61
Time spent using electronic devices by children at 3.5 years (hours/week)								
<= 2 hours	Ref		Ref		Ref		Ref	
] 2 ; 4] hours	-0.53 [-0.91 ; -0.15]	<0.01	-0.15 [-0.38 ; 0.08]	0.19	-0.31 [-0.83 ; 0.20]	0.23	-0.34 [-0.63 ; -0.04]	0.02
>4 hours	-0.21 [-0.56 ; 0.13]	0.23	-0.04 [-0.25 ; 0.16]	0.69	-0.01 [-0.47 ; 0.46]	0.98	-0.30 [-0.57 ; -0.04]	0.03
Number of windows in the child's room								
1	Ref		Ref		Ref		Ref	
2	0.41 [-0.01 ; 0.83]	0.06	0.19 [-0.06 ; 0.44]	0.13	0.19 [-0.38 ; 0.76]	0.51	-0.14 [-0.47 ; 0.19]	0.40
Ventilation in the child's room								
Yes	Ref		Ref		Ref		Ref	
No	-0.36 [-0.69 ; -0.03]	0.03	-0.11 [-0.31 ; 0.08]	0.26	-0.39 [-0.83 ; 0.05]	0.08	-0.23 [-0.49 ; 0.02]	0.07
Environmental								
Season of children's hair sampling at 3.5 years								
Autumn	Ref		Ref		Ref		Ref	
Winter	-0.54 [-0.84 ; -0.25]	<0.01	-0.04 [-0.22 ; 0.14]	0.65	-0.04 [-0.44 ; 0.37]	0.85	-0.25 [-0.48 ; -0.01]	0.04

Table S5. Unweighted results of association between OPFR concentrations and potential determinants among mothers (n=388) at birth in France (2011).

OPFR determinants	EHDPP		TBEP		TBP		TCEP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P
Home renovation work before birth								
No	Ref		Ref		Ref		Ref	
Yes	0.11 [-0.08 ; 0.30]	0.26	0.05 [-0.09 ; 0.19]	0.49	-0.06 [-0.14 ; 0.02]	0.12	-0.06 [-0.30 ; 0.18]	0.63
Mothers' BDE 47 concentration at birth (ng/g)								
<= 0.43	Ref		Ref		Ref		Ref	
] 0.43 ; 1.23]	0.24 [-0.07 ; 0.54]	0.13	0.01 [-0.23 ; 0.24]	0.99	-0.03 [-0.15 ; 0.10]	0.66	-0.01 [-0.39 ; 0.38]	0.97
>1.23	0.29 [0.04 ; 0.54]	0.02	-0.04 [-0.23 ; 0.14]	0.64	0.04 [-0.06 ; 0.14]	0.47	0.39 [0.08 ; 0.71]	0.02
Mothers' BDE 209 concentration at birth (ng/g)								
<= 5.4	Ref		Ref		Ref		Ref	
] 5.4 ; 11.8]	0.18 [-0.05 ; 0.40]	0.13	0.06 [-0.11 ; 0.24]	0.46	0.13 [0.04 ; 0.22]	<0.01	0.21 [-0.09 ; 0.50]	0.17
>11.8	0.46 [0.23 ; 0.68]	<0.01	0.18 [0.01 ; 0.35]	0.04	0.14 [0.05 ; 0.23]	<0.01	0.32 [0.03 ; 0.61]	0.03
Pre-pregnancy BMI								
18.5 - < 25	Ref		Ref		Ref		Ref	
<18.5	-0.21 [-0.56 ; 0.13]	0.22	-0.11 [-0.36 ; 0.15]	0.42	0.03 [-0.11 ; 0.17]	0.63	-0.44 [-0.88 ; 0.00]	0.05
25 - < 30	-0.01 [-0.29 ; 0.26]	0.91	-0.14 [-0.35 ; 0.05]	0.15	0.06 [-0.05 ; 0.17]	0.27	-0.20 [-0.55 ; 0.14]	0.24
30 or more	0.26 [-0.10 ; 0.61]	0.15	0.13 [-0.13 ; 0.39]	0.32	0.14 [0.00 ; 0.28]	0.05	0.12 [-0.32 ; 0.57]	0.58
Mother's level of education at birth								
<= BAC	Ref		Ref		Ref		Ref	
BAC +2	-0.13 [-0.39 ; 0.13]	0.33	0.09 [-0.10 ; 0.29]	0.34	-0.02 [-0.12 ; 0.09]	0.71	0.01 [-0.32 ; 0.34]	0.94
> BAC	-0.10 [-0.33 ; 0.13]	0.39	0.13 [-0.04 ; 0.29]	0.15	-0.05 [-0.13 ; 0.06]	0.51	0.09 [-0.20 ; 0.38]	0.54
Household income at birth (euros)								
<=2999	Ref		Ref		Ref		Ref	
[3000 ; 3999]	0.19 [-0.05 ; 0.42]	0.12	0.03 [-0.45 ; 0.21]	0.71	-0.03 [-0.13 ; 0.08]	0.86	-0.04 [-0.34 ; 0.26]	0.79
> 4000	-0.02 [-0.25 ; 0.21]	0.88	0.20 [0.03 ; 0.36]	0.02	-0.04 [-0.13 ; 0.10]	0.91	0.29 [-0.01 ; 0.57]	0.05
Season of mothers' hair								

Table S5. Unweighted results of association between OPFR concentrations and potential determinants among mothers (n=388) at birth in France (2011).

sampling									
Autumn	Ref		Ref		Ref		Ref		
Summer	0.22 [0.01 ; 0.42]	0.04	-0.12 [-0.27 ; 0.03]	0.11	0.01 [-0.08 ; 0.09]	0.96	-0.07 [-0.33 ; 0.19]	0.59	
Number of people in the household at birth									
<=3 persons	Ref		Ref		Ref		Ref		
4 persons	0.12 [-0.09 ; 0.33]	0.27	0.12 [-0.04 ; 0.27]	0.13	-0.01 [-0.09 ; 0.08]	0.86	0.07 [-0.19 ; 0.34]	0.59	
>5 persons	0.25 [-0.01 ; 0.52]	0.06	0.12 [-0.08 ; 0.31]	0.24	-0.01 [-0.11 ; 0.10]	0.91	-0.04 [-0.38 ; 0.29]	0.81	

OPFR determinants	TCPP		TDCPP		TEP		TMCP		TPP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P
Sources										
Home renovation work before birth										
No	Ref		Ref		Ref		Ref		Ref	
Yes	-0.01 [-0.15 ; 0.14]	0.94	-0.18 [-0.44 ; 0.08]	0.17	-0.08 [-0.24 ; 0.08]	0.34	-0.26 [-0.56 ; 0.04]	0.09	-0.18 [-0.37 ; 0.01]	0.06
Mothers' BDE 47 concentration at birth (ng/g)										
<= 0.43	Ref		Ref		Ref		Ref		Ref	
] 0.43 ; 1.23]	-0.06 [-0.30 ; 0.17]	0.59	-0.06 [-0.49 ; 0.36]	0.76	-0.13 [-0.38 ; 0.13]	0.34	0.52 [0.03 ; 1.00]	0.04	-0.01 [-0.32 ; 0.30]	0.95
>1.23	0.26 [0.07 ; 0.45]	<0.01	0.13 [-0.22 ; 0.48]	0.46	0.04 [-0.17 ; 0.25]	0.72	0.42 [0.02 ; 0.81]	0.04	0.21 [-0.05 ; 0.46]	0.11
Mothers' BDE 209 concentration at birth (ng/g)										
<= 5.4	Ref		Ref		Ref		Ref		Ref	
] 5.4 ; 11.8]	0.16 [-0.02 ; 0.34]	0.07	0.61 [0.31 ; 0.90]	<0.01	0.04 [-0.15 ; 0.24]	0.66	0.38 [0.02 ; 0.73]	0.04	0.26 [0.03 ; 0.49]	0.03
>11.8	0.13 [-0.05 ; 0.31]	0.15	1.25 [0.96 ; 1.54]	<0.01	0.17 [-0.02 ; 0.36]	0.08	0.95 [0.60 ; 1.30]	<0.01	0.59 [0.36 ; 0.82]	<0.01
Socio-demographic										
Pre-pregnancy BMI										
18.5 - < 25	Ref		Ref		Ref		Ref		Ref	
<18.5	-0.15 [-0.42 ; 0.11]	0.26	-0.31 [-0.79 ; 0.17]	0.20	0.04 [-0.26 ; 0.33]	0.81	-0.20 [-0.75 ; 0.35]	0.47	-0.49 [-0.84 ; -0.13]	<0.01
25 - < 30	0.25 [-0.46 ; -0.04]	0.02	-0.28 [-0.66 ; 0.09]	0.13	0.12 [-0.11 ; 0.35]	0.31	-0.23 [-0.66 ; 0.19]	0.28	-0.25 [-0.53 ; 0.02]	0.06
30 or more	-0.00 [-0.27 ; 0.27]	0.98	0.26 [-0.23 ; 0.74]	0.29	0.06 [-0.24 ; 0.35]	0.71	0.22 [-0.34 ; 0.78]	0.44	0.25 [-0.10 ; 0.61]	0.16
Mother's level of education at birth										
<= BAC	Ref		Ref		Ref		Ref		Ref	
BAC +2	0.17 [-0.03 ; 0.37]	0.09	0.04 [-0.31 ; 0.41]	0.80	-0.01 [-0.22 ; 0.21]	0.97	-0.13 [-0.54 ; 0.28]	0.53	-0.09 [-0.35 ; 0.18]	0.52
> BAC	0.23 [0.05 ; 0.40]	0.02	0.08 [-0.24 ; 0.40]	0.62	-0.04 [-0.24 ; 0.15]	0.65	-0.02 [-0.38 ; 0.35]	0.93	-0.05 [-0.29 ; 0.18]	0.66
Household income at birth (euros)										
<=2999	Ref		Ref		Ref		Ref		Ref	
[3000 ; 3999]	0.15 [-0.03 ; 0.33]	0.09	0.13 [-0.31 ; 0.34]	0.94	-0.07 [-0.26 ; 0.12]	0.47	-0.23 [-0.61 ; 0.14]	0.22	0.07 [-0.17 ; 0.31]	0.54
> 4000	0.20 [0.02 ; 0.37]	0.03	0.06 [-0.26 ; 0.37]	0.72	-0.31 [-0.50 ; -0.12]	<0.01	-0.30 [-0.66 ; 0.06]	0.11	-0.04 [-0.27 ; 0.19]	0.73
Environmental										

Table S5. Unweighted results of association between OPFR concentrations and potential determinants among mothers (n=388) at birth in France (2011).

Season of mothers' hair sampling										
Autumn	Ref		Ref		Ref		Ref		Ref	
Summer	0.02 [-0.13 ; 0.18]	0.76	0.08 [-0.20 ; 0.36]	0.56	0.04 [-0.13 ; 0.21]	0.65	0.46 [0.04 ; 0.68]	0.03	0.08 [-0.13 ; 0.29]	0.45
Number of people in the household at birth										
<=3 persons	Ref		Ref		Ref		Ref		Ref	
4 persons	0.01 [-0.15 ; 0.18]	0.86	-0.03 [-0.32 ; 0.26]	0.82	-0.08 [-0.25 ; 0.10]	0.38	-0.21 [-0.54 ; 0.12]	0.22	-0.02 [-0.24 ; 0.19]	0.83
>5 persons	0.02 [-0.19 ; 0.22]	0.88	0.02 [-0.34 ; 0.39]	0.89	-0.01 [-0.21 ; 0.23]	0.91	-0.12 [-0.54 ; 0.29]	0.57	-0.14 [-0.41 ; 0.13]	0.30

Table S6. Unweighted results of association between OPFR concentrations and potential determinants among children (n=259) at 3.5 years old in France (2014-2015).

OPFR determinants	EHDPP		TBEP		TBP		TCEP		TCPP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P	β [IC95%]	P
Sources										
Home renovation work at 3.5 years of child during the year before the survey										
No	ref		ref		ref		ref		ref	
Yes	-0.27 [-0.58 ; 0.03]	0.06	0.03 [-0.33 ; 0.38]	0.88	-0.04 [-0.16 ; 0.08]	0.54	0.27 [0.01 ; 0.53]	0.04	-0.04 [-0.26 ; 0.19]	0.74
Residential home year construction at 3.5 years of child										
>2000	ref		ref		ref		ref		ref	
[1970-2000]	-0.04 [-0.40 ; 0.32]	0.83	0.34 [-0.07 ; 0.75]	0.11	0.06 [-0.10 ; 0.20]	0.53	0.18 [-0.12 ; 0.49]	0.24	0.26 [-0.01 ; 0.52]	0.06
<1970	0.01 [-0.32 ; 0.34]	0.97	0.15 [-0.23 ; 0.53]	0.44	-0.01 [-0.17 ; 0.14]	0.86	0.27 [-0.02 ; 0.55]	0.06	0.23 [-0.02 ; 0.47]	0.07
Type of floor in the child's room										
Tile	ref		ref		ref		ref		ref	
Lino	0.10 [-0.49 ; 0.69]	0.74	0.64 [-0.04 ; 1.32]	0.07	-0.03 [-0.26 ; 0.21]	0.83	-0.02 [-0.53 ; 0.48]	0.92	0.31 [-0.13 ; 0.76]	0.16
Carpet	0.81 [0.05 ; 1.57]	0.03	0.61 [-0.27 ; 1.49]	0.17	0.03 [-0.28 ; 0.33]	0.87	0.81 [0.16 ; 1.47]	0.01	0.11 [-0.46 ; 0.69]	0.70
Parquet	0.24 [-0.25 ; 0.74]	0.33	0.60 [0.03 ; 1.17]	0.04	-0.02 [-0.22 ; 0.17]	0.82	0.09 [-0.33 ; 0.51]	0.68	0.27 [-0.11 ; 0.64]	0.16
Duration of breastfeeding (months)										
<= 1	ref		ref		ref		ref		ref	
] 1 ; 4]	-0.01 [-0.35 ; 0.33]	0.97	0.13 [-0.27 ; 0.53]	0.52	-0.03 [-0.17 ; 0.10]	0.63	-0.04 [-0.34 ; 0.26]	0.78	0.08 [-0.18 ; 0.34]	0.54
>4	0.09 [-0.25 ; 0.43]	0.60	0.36 [-0.04 ; 0.75]	0.06	-0.02 [-0.15 ; 0.12]	0.79	-0.03 [-0.33 ; 0.27]	0.84	0.14 [-0.11 ; 0.40]	0.27
Children's BDE 47 concentration at 3.5 years (ng/g)										
<= 0.43	ref		ref		ref		ref		ref	
] 0.43 ; 1.23]	0.03 [-0.31 ; 0.38]	0.86	-0.03 [-0.43 ; 0.37]	0.87	0.02 [-0.12 ; 0.15]	0.82	-0.01 [-0.30 ; 0.30]	0.99	0.15 [-0.11 ; 0.41]	0.26
>1.23	0.26 [-0.09 ; 0.61]	0.14	-0.34 [-0.74 ; 0.06]	0.10	0.05 [-0.08 ; 0.19]	0.44	-0.07 [-0.37 ; 0.23]	0.65	0.33 [0.07 ; 0.59]	0.01
Socio-demographic										
Mother's education level at 3.5 years of child										
<= BAC	ref		ref		ref		ref		ref	
BAC +2	0.36 [-0.06 ; 0.77]	0.09	0.11 [-0.37 ; 0.59]	0.65	-0.01 [-0.17 ; 0.16]	0.96	-0.21 [-0.57 ; 0.15]	0.25	0.09 [-0.22 ; 0.41]	0.56
> BAC	0.12 [-0.23 ; 0.47]	0.49	0.26 [-0.15 ; 0.66]	0.21	-0.10 [-0.24 ; 0.03]	0.14	-0.17 [-0.47 ; 0.14]	0.28	-0.02 [-0.28 ; 0.24]	0.88
Household income at 3.5 years of child (euros)										
<=2999	ref		ref		ref		ref		ref	
[3000 ; 3999]	-0.14 [-0.54 ; 0.26]	0.49	-0.02 [-0.48 ; 0.45]	0.94	-0.21 [-0.37 ; -0.06]	<0.01	-0.19 [-0.54 ; 0.15]	0.27	-0.18 [-0.48 ; 0.12]	0.24
> 4000	0.09 [-0.27 ; 0.44]	0.64	0.23 [-0.18 ; 0.64]	0.27	-0.16 [-0.30 ; -0.02]	0.02	-0.13 [-0.44 ; 0.17]	0.39	-0.08 [-0.35 ; 0.19]	0.57
Number of persons in the household at 3.5 years of child										
<= 3 persons	ref		ref		ref		ref		ref	
4 persons	-0.27 [-0.61 ; 0.08]	0.14	-0.16 [-0.57 ; 0.25]	0.43	-0.06 [-0.20 ; 0.07]	0.36	-0.03 [-0.33 ; 0.28]	0.86	-0.15 [-0.42 ; 0.11]	0.26
>5 persons	0.03 [-0.36 ; 0.42]	0.88	0.09 [-0.37 ; 0.55]	0.70	-0.11 [-0.26 ; 0.05]	0.17	0.04 [-0.30 ; 0.38]	0.83	-0.20 [-0.50 ; 0.09]	0.18
Pre-pregnancy BMI										

Table S6. Unweighted results of association between OPFR concentrations and potential determinants among children (n=259) at 3.5 years old in France (2014-2015).

18.5 - < 25	ref		ref		ref		ref		ref	
<18.5	-0.14 [-0.70 ; 0.42]	0.63	-0.75 [-1.40 ; -0.10]	0.02	0.09 [-0.13 ; 0.31]	0.42	-0.06 [-0.55 ; 0.43]	0.80	0.33 [-0.09 ; 0.76]	0.12
25 - < 30	0.05 [-0.35 ; 0.45]	0.82	-0.19 [-0.65 ; 0.27]	0.42	0.06 [-0.10 ; 0.22]	0.47	0.06 [-0.29 ; 0.40]	0.75	-0.09 [-0.09 ; 0.76]	0.55
30 ou plus	0.56 [0.02 ; 1.11]	0.04	-0.45 [-1.08 ; 0.18]	0.16	0.08 [-0.13 ; 0.30]	0.46	0.16 [-0.32 ; 0.63]	0.51	0.04 [-0.37 ; 0.45]	0.85
Behavioural										
Time spent outside by children at age 3.5 years (hours/week)										
<= 4.5 hours	ref		ref		ref		ref		ref	
] 4.5 ; 7] hours	0.11 [-0.23 ; 0.44]	0.53	0.04 [-0.34 ; 0.44]	0.80	-0.13 [-0.26 ; 0.01]	0.06	0.19 [-0.09 ; 0.48]	0.20	0.03 [-0.23 ; 0.28]	0.84
>7hours	0.24 [-0.12 ; 0.61]	0.19	-0.15 [-0.57 ; 0.27]	0.49	-0.05 [-0.19 ; 0.09]	0.49	-0.06 [-0.38 ; 0.25]	0.69	0.04 [-0.24 ; 0.31]	0.79
Time spent using electronic devices by children at 3.5 years (hours/week)										
<= 2 hours	ref		ref		ref		ref		ref	
] 2 ; 4] hours	0.01 [-0.35 ; 0.36]	0.99	-0.27 [-0.67 ; 0.13]	0.19	-0.01 [-0.14 ; 0.13]	0.91	-0.29 [-0.58 ; 0.01]	0.06	-0.12 [-0.38 ; 0.15]	0.38
>4 hours	-0.07 [-0.41 ; 0.28]	0.71	-0.18 [-0.58 ; 0.21]	0.36	0.03 [-0.10 ; 0.17]	0.63	-0.01 [-0.29 ; 0.29]	0.98	0.03 [-0.23 ; 0.28]	0.82
Number of windows in the child's room										
1	ref		ref		ref		ref		ref	
2	-0.01 [-0.40 ; 0.39]	0.92	0.12 [-0.34 ; 0.58]	0.61	0.03 [-0.12 ; 0.19]	0.63	0.42 [0.09 ; 0.76]	0.01	0.20 [-0.10 ; 0.50]	0.18
Ventilation in the child's room										
Yes	ref		ref		ref		ref		ref	
No	-0.08 [-0.39 ; 0.23]	0.62	0.23 [-0.13 ; 0.59]	0.21	0.01 [-0.11 ; 0.13]	0.89	-0.02 [-0.29 ; 0.25]	0.86	0.15 [-0.08 ; 0.39]	0.20
Environmental										
Season of children's hair sampling at 3.5 years										
Autumn	ref		ref		ref		ref		ref	
Winter	0.01 [-0.29 ; 0.32]	0.92	-0.14 [-0.49 ; 0.20]	0.41	-0.08 [-0.19 ; 0.03]	0.19	-0.08 [-0.34 ; 0.18]	0.54	-0.12 [-0.35 ; 0.10]	0.29

OPFR determinants	TDCPP		TEP		TMCP		TPP	
	β [IC95%]	P	β [IC95%]	P	β [IC95%]		β [IC95%]	P
Sources								
Home renovation work at 3.5 years of child during the year before the survey								
No	ref		ref		ref		ref	
Yes	0.23 [-0.08 ; 0.54]	0.15	0.09 [-0.09 ; 0.27]	0.34	-0.29 [-0.72 ; 0.12]	0.17	-0.01 [-0.26 ; 0.23]	0.90
Residential home year construction at 3.5 years of child								
>2000	ref		ref		ref		ref	
]1970-2000]	0.05 [-0.31 ; 0.42]	0.78	-0.05 [-0.26 ; 0.16]	0.63	0.46 [-0.03 ; 0.95]	0.07	0.08 [-0.20 ; 0.36]	0.58
<1970	0.09 [-0.25 ; 0.43]	0.60	0.12 [-0.07 ; 0.32]	0.21	0.54 [0.09 ; 0.99]	0.01	0.21 [-0.05 ; 0.47]	0.12
Type of floor in the child's room								
Tile	ref		ref		ref		ref	
Lino	-0.09 [-0.70 ; 0.51]	0.76	0.32 [-0.01 ; 0.69]	0.06	0.60 [-0.22 ; 1.41]	0.15	0.33 [-0.13 ; 0.80]	0.16
Carpet	-0.15 [-0.94 ; 0.63]	0.70	-0.12 [-0.57 ; 0.32]	0.59	0.45 [-0.61 ; 1.51]	0.40	0.44 [-0.17 ; 1.05]	0.15
Parquet	-0.13 [-0.63 ; 0.38]	0.63	0.06 [-0.23 ; 0.35]	0.68	0.28 [-0.40 ; 0.97]	0.42	0.18 [-0.21 ; 0.87]	0.36

Table S6. Unweighted results of association between OPFR concentrations and potential determinants among children (n=259) at 3.5 years old in France (2014-2015).

Duration of breastfeeding (months)									
<= 1	ref		ref		ref		ref		
] 1 ; 4]	-0.10 [-0.45 ; 0.25]	0.57	-0.10 [-0.30 ; 0.10]	0.31	-0.23 [-0.70 ; 0.24]	0.38	0.05 [-0.22 ; 0.33]	0.70	
>4	-0.09 [-0.44 ; 0.26]	0.62	-0.26 [-0.46 ; 0.07]	<0.01	0.21 [-0.26 ; 0.68]	0.35	0.03 [-0.25 ; 0.30]	0.85	
Children's BDE 47 concentration at 3.5 years(ng/g)									
<= 0.43	ref		ref		ref		ref		
] 0.43 ; 1.23]	0.19 [-0.16 ; 0.54]	0.28	0.13 [-0.08 ; 0.33]	0.22	0.05 [-0.43 ; 0.52]	0.85	0.28 [0.01 ; 0.55]	0.04	
>1.23	0.40 [0.05 ; 0.75]	0.02	0.07 [-0.13 ; 0.27]	0.51	0.24 [-0.24 ; 0.72]	0.32	0.24 [-0.03 ; 0.51]	0.08	
Socio-demographic									
Mother's education level at 3.5 years of child									
<= BAC	ref		ref		ref		ref		
BAC +2	-0.09 [-0.51 ; 0.32]	0.65	0.04 [-0.20 ; 0.28]	0.74	0.03 [-0.55 ; 0.60]	0.93	0.11 [-0.22 ; 0.44]	0.52	
> BAC	-0.46 [-0.81 ; -0.11]	0.01	-0.19 [-0.40 ; 0.01]	0.06	0.03 [-0.45 ; 0.52]	0.88	0.09 [-0.18 ; 0.37]	0.51	
Household income at 3.5 years of child (euros)									
<=2999	ref		ref		ref		ref		
]3000 ; 3999]	-0.16 [-0.57 ; 0.25]	0.44	-0.27 [-0.50 ; -0.03]	0.03	0.06 [-0.49 ; 0.62]	0.82	-0.09 [-0.42 ; 0.23]	0.55	
> 4000	-0.30 [-0.66 ; 0.07]	0.11	-0.24 [-0.44 ; -0.03]	0.03	-0.21 [-0.71 ; 0.28]	0.40	-0.03 [-0.31 ; 0.26]	0.86	
Number of persons in the household at 3.5 years of child									
<= 3 persons	ref		ref		ref		ref		
4 persons	-0.12 [-0.47 ; 0.24]	0.52	-0.07 [-0.28 ; 0.14]	0.51	-0.47 [-0.95 ; 0.01]	0.06	-0.18 [-0.46 ; 0.10]	0.20	
>5 persons	0.25 [-0.15 ; 0.66]	0.21	0.03 [-0.21 ; 0.26]	0.85	-0.46 [-1.00 ; 0.09]	0.13	-0.03 [-0.34 ; 0.29]	0.87	
Pre-pregnancy BMI									
18.5 - < 25	ref		ref		ref		ref		
<18.5	-0.10 [-0.67 ; 0.48]	0.74	0.08 [0.24 ; 0.41]	0.61	-0.27 [-1.05 ; 0.51]	0.49	0.33 [0.11 ; 0.78]	0.14	
25 - < 30	0.18 [-0.23 ; 0.60]	0.37	0.32 [0.10 ; 0.56]	<0.01	0.06 [-0.50 ; 0.61]	0.84	0.07 [-0.25 ; 0.39]	0.65	
30 ou plus	0.18 [-0.38 ; 0.74]	0.53	-0.04 [-0.36 ; 0.28]	0.82	0.45 [-0.31 ; 1.22]	0.24	0.10 [-0.33 ; 0.54]	0.64	
Behavioural									
Time spent outside by children at age 3.5 years (hours/week)									
<= 4.5 hours	ref		ref		ref		ref		
] 4.5 ; 7] hours	0.44 [0.10 ; 0.78]	0.01	-0.05 [-0.25 ; 0.14]	0.59	0.34 [-0.12 ; 0.80]	0.15	0.20 [-0.06 ; 0.47]	0.13	
>7hours	0.43 [0.06 ; 0.79]	0.02	-0.15 [-0.36 ; 0.07]	0.18	-0.09 [-0.58 ; 0.43]	0.74	-0.01 [-0.29 ; 0.28]	0.99	
Time spent using electronic devices by children at 3.5 years (hours/week)									
<= 2 hours	ref		ref		ref		ref		
] 2 ; 4] hours	-0.21 [-0.56 ; 0.15]	0.25	-0.12 [-0.33 ; 0.08]	0.23	-0.24 [-0.72 ; 0.23]	0.32	-0.16 [-0.43 ; 0.12]	0.26	
>4 hours	-0.10 [-0.44 ; 0.25]	0.58	0.01 [-0.19 ; 0.21]	0.90	0.02 [-0.45 ; 0.49]	0.93	-0.12 [-0.39 ; 0.15]	0.39	
Number of windows in the child's room									
1	ref		ref		ref		ref		
2	0.40 [0.01 ; 0.82]	0.04	0.01 [-0.17 ; 0.20]	0.88	0.11 [-0.44 ; 0.66]	0.69	-0.02 [-0.33 ; 0.30]	0.91	
Ventilation in the child's room									
Yes	ref		ref		ref		ref		
No	-0.12 [-0.44 ; 0.20]	0.45	0.17 [-0.05 ; 0.41]	0.13	-0.06 [-0.49 ; 0.38]	0.79	-0.10 [-0.35 ; 0.15]	0.43	
Environmental									
Season of children's hair sampling at 3.5 years									
Autumn	ref		ref		ref		ref		
Winter	-0.29 [-0.60 ; 0.01]	0.06	-0.08 [-0.25 ; 0.10]	0.37	0.08 [-0.33 ; 0.49]	0.72	0.13 [-0.37 ; 0.11]	0.29	

Table S7. PBDE and PCB concentrations (ng/g) in mothers' hair at birth in 2011 and in children hair aged 3.5 years old in 2014-2015 in France.

Substances	CAS number	% > LOD	Populations	Min	P25	P50	P75	P95	Max	Geometric mean (SD)
BDE 28	41318-75-6	11.49	Mothers	-	-	-	-	-	-	-
		1.9	Children	-	-	-	-	-	-	-
BDE 47	5436-43-1	47.26	Mothers	0.02	0.86	2.51	8.35	42	498	2.47 (1.18)
		21.6	Children	0.04	0.27	0.6	1.66	6.55	26	0.66 (1.17)
BDE 85	182346-21-0	0.26	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 99	60348-60-9	18.28	Mothers	-	-	-	-	-	-	-
		4.2	Children	-	-	-	-	-	-	-
BDE 100	189084-64-8	3.13	Mothers	-	-	-	-	-	-	-
		0.4	Children	-	-	-	-	-	-	-
BDE 119	189084-66-0	0	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 153	68631-49-2	7.31	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 154	207122-15-4	1.04	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 209	1163-19-5		Mothers	0.17	4.33	7.8	17	61	452	8.39 (1.11)
PCB 28	7012-37-5	99.48	Mothers	0.2	0.83	1.26	5.87	11	23	1.79 (1.09)
		91.1	Children	0.06	0.39	0.56	1.24	2.96	5.66	0.7 (1.10)
PCB 31	16606-02-3	99.48	Mothers	0.2	0.92	1.3	6.53	13	26	1.96 (1.10)
		95	Children	0.06	0.38	0.64	1.34	3.91	7.25	0.73 (1.11)
PCB 52	35693-99-3	100	Mothers	0.23	1.36	2.02	6.36	13	27	2.61 (1.09)
		96.5	Children	0.06	0.51	0.88	1.44	3.12	8.31	0.84 (1.09)
PCB 77	32598-13-3	0	Mothers	-	-	-	-	-	-	-
		1.1	Children	-	-	-	-	-	-	-

PCB 101	37680-73-2	99.74	Mothers	0.22	1.20	1.83	2.94	6.26	18	1.88 (1.06)
		95.4	Children	0.09	0.51	0.8	1.28	2.3	9.19	0.78 (1.08)
PCB 105	32598-14-4	6.53	Mothers	-	-	-	-	-	-	-
		6.5	Children	-	-	-	-	-	-	-
PCB 118	31508-00-6	26.9	Mothers	0.61	0.67	0.7	0.77	1.66	33	0.83 (1.03)
		9.6	Children	-	-	-	-	-	-	-
PCB 126	57465-28-8	0.5	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
PCB 138	35065-28-2	9.7	Mothers	-	-	-	-	-	-	-
		3.8	Children	-	-	-	-	-	-	-
PCB 153	35065-27-1	0.26	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
PCB 180	35065-29-3	4.96	Mothers	-	-	-	-	-	-	-
		2.3	Children	-	-	-	-	-	-	-

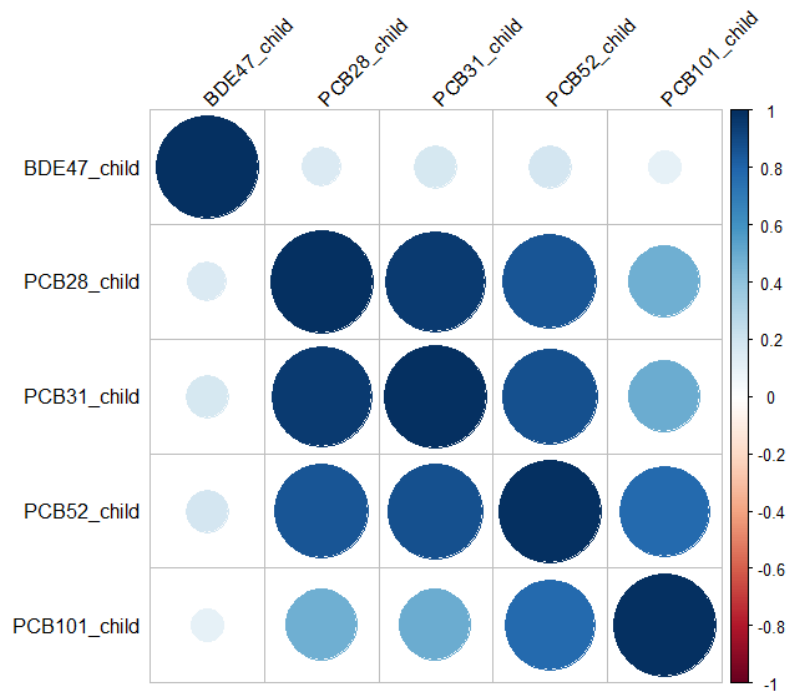


Fig S8. Weighted correlation matrix of PBDE and PCB concentrations among children in France (2014-2015).

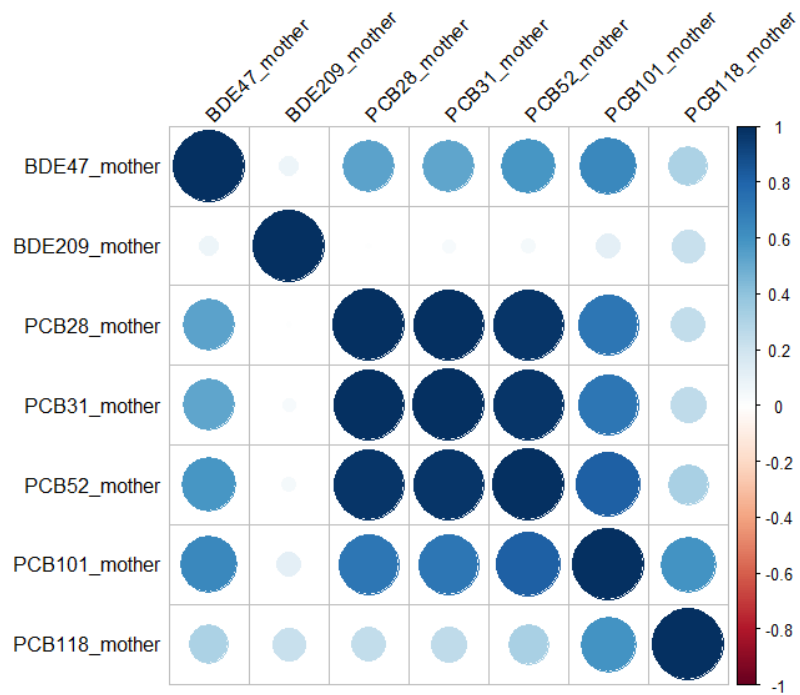


Fig S9. Weighted correlation matrix of PBDE and PCB concentrations among mothers in France (2011).

Table S8. Unweighted PBDE and PCB concentrations (ng/g) in mothers at birth (n=388) in 2011 and in children aged 3.5 years old (n=259) in 2014-2015.

Substances	CAS number	% > LOD	Populations	Min	P25	P50	P75	P95	Max	Geometric mean (SD)
BDE 28	41318-75-6	11.49	Mothers	-	-	-	-	-	-	-
		1.9	Children	-	-	-	-	-	-	-
BDE 47	5436-43-1	47.26	Mothers	0.018	0.67	1.83	5.67	28.56	498	1.86 (5.75)
		21.6	Children	0.04	0.3	0.72	1.69	6.26	26.3	0.71 (3.43)
BDE 85	182346-21-0	0.26	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 99	60348-60-9	18.28	Mothers	-	-	-	-	-	-	-
		4.2	Children	-	-	-	-	-	-	-
BDE 100	189084-64-8	3.13	Mothers	-	-	-	-	-	-	-
		0.4	Children	-	-	-	-	-	-	-
BDE 119	189084-66-0	0	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 153	68631-49-2	7.31	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 154	207122-15-4	1.04	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
BDE 209	1163-19-5		Mothers	0.17	4.4	7.9	15.8	57.73	452	8.22 (3.36)
			Children	-	-	-	-	-	-	-
PCB 28	7012-37-5	99.48	Mothers	0.2	0.75	1.17	2.18	10.57	23.56	1.52 (2.76)
		91.1	Children	0.06	0.34	0.55	1.05	3.44	5.66	0.62 (2.50)
PCB 31	16606-02-3	99.48	Mothers	0.2	0.8	1.24	2.50	12.31	25.98	1.65 (2.89)
		95	Children	0.06	0.33	0.54	1.03	3.92	7.25	0.65 (2.48)
PCB 52	35693-99-3	100	Mothers	0.23	1.28	1.87	3.4	12.6	26.88	2.29 (2.46)
		96.5	Children	0.06	0.46	0.78	1.29	3.18	8.31	0.81 (2.23)
PCB 77	32598-13-3	0	Mothers	-	-	-	-	-	-	-

		1.1	Children	-	-	-	-	-	-	-
PCB 101	37680-73-2	99.74	Mothers	0.22	1.14	1.77	2.66	5.4	18.51	1.76 (1.97)
		95.4	Children	0.09	0.5	0.75	1.32	2.56	9.19	0.77 (2.12)
PCB 105	32598-14-4	6.53	Mothers	-	-	-	-	-	-	-
		6.5	Children	-	-	-	-	-	-	-
PCB 118	31508-00-6	26.9	Mothers	0.61	0.67	0.70	1	1.7	32.7	0.84 (1.47)
		9.6	Children	-	-	-	-	-	-	-
PCB 126	57465-28-8	0.5	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
PCB 138	35065-28-2	9.7	Mothers	-	-	-	-	-	-	-
		3.8	Children	-	-	-	-	-	-	-
PCB 153	35065-27-1	0.26	Mothers	-	-	-	-	-	-	-
		0	Children	-	-	-	-	-	-	-
PCB 180	35065-29-3	4.96	Mothers	-	-	-	-	-	-	-
		2.3	Children	-	-	-	-	-	-	-

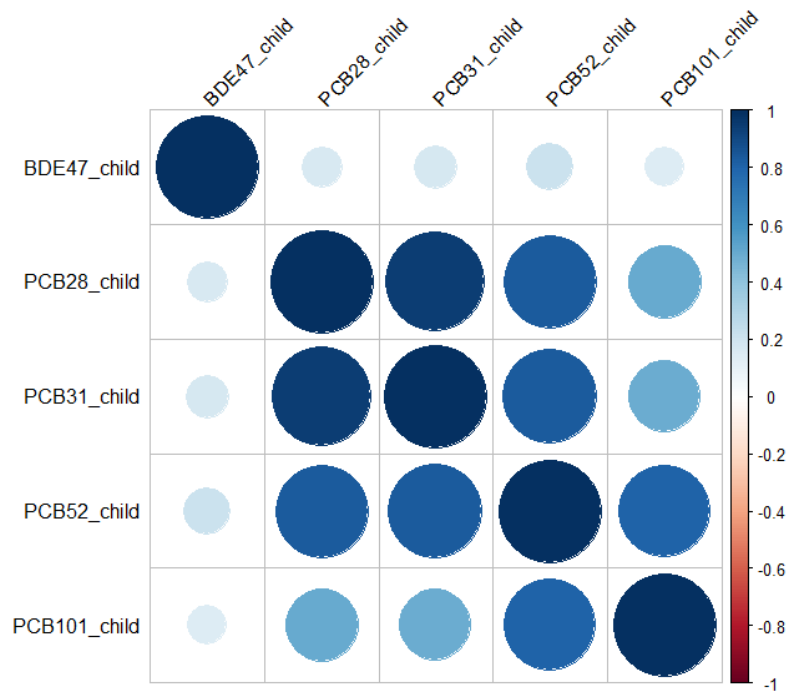


Fig S10. Unweighted correlation matrix of PBDE and PCB concentrations among children (n=259) in France (2014-2015).

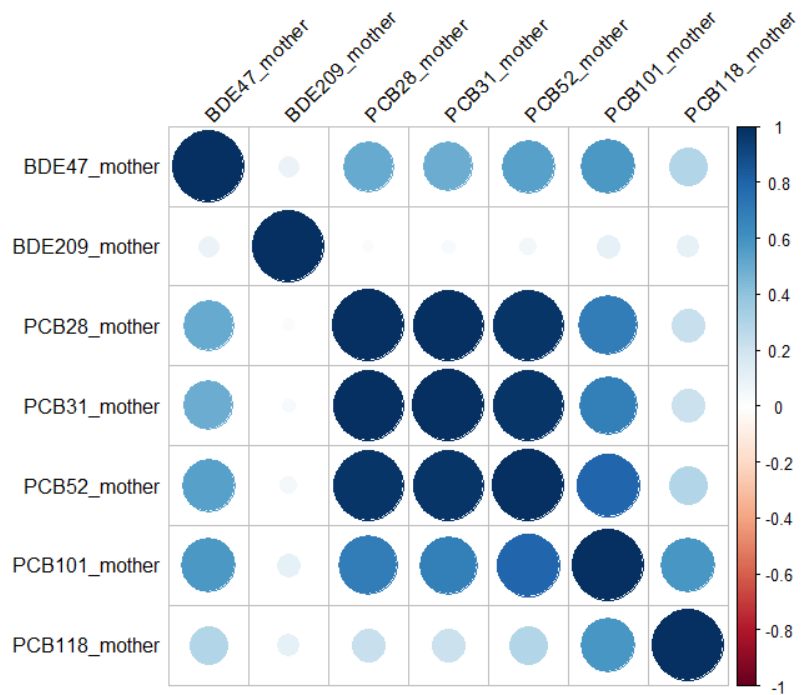


Fig S11. Unweighted correlation matrix of PBDE and PCB concentrations among mothers (n=388) in France (2011).

Annexe: Matériel supplémentaire de l'article « Early-life exposure to organophosphate flame retardants and child neurodevelopment, in a French national birth cohort.»

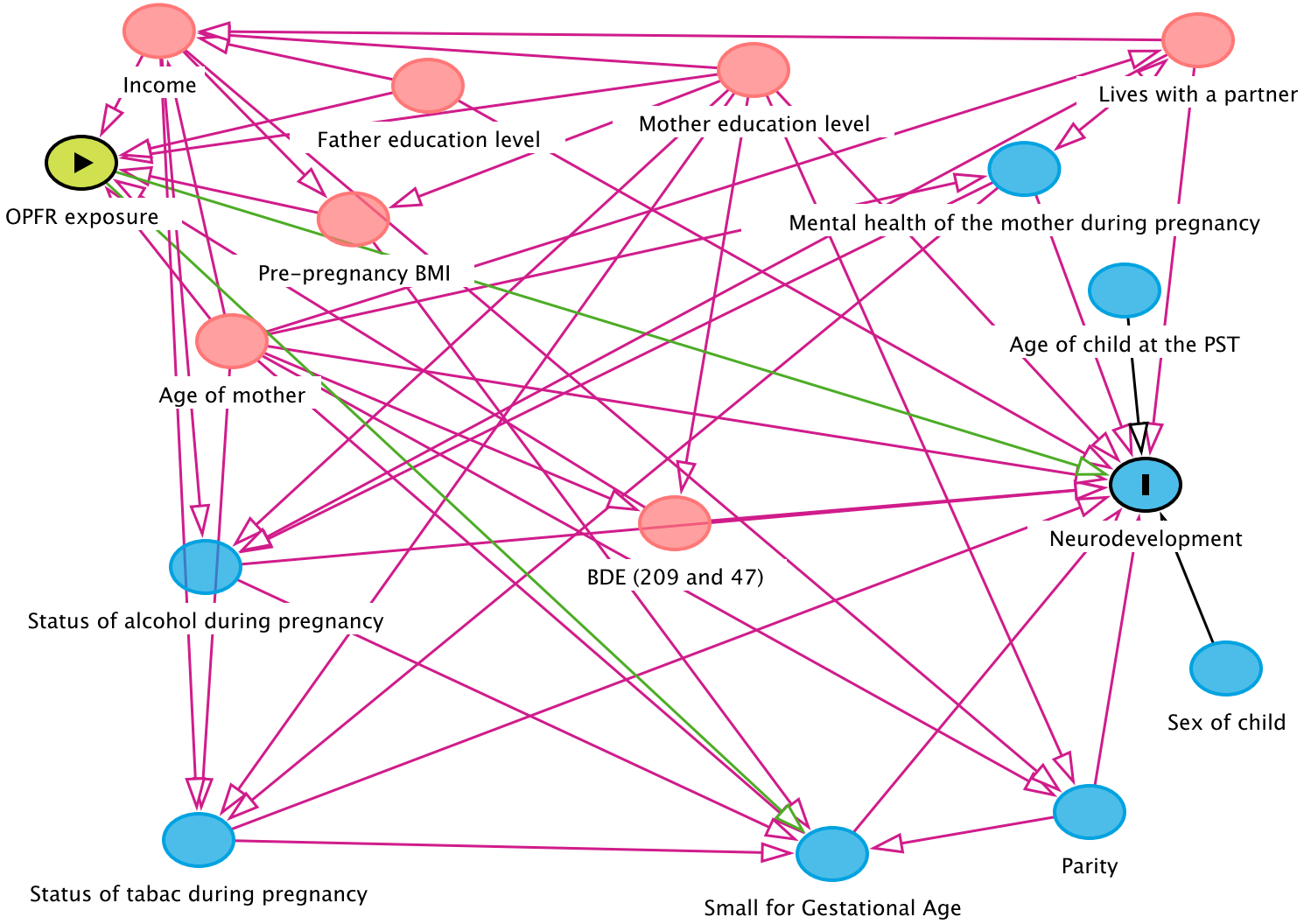


Table S1. Association between OPFR prenatal exposure and score of PST

OPFR		β	IC 95 %
EHDPP*		-0.45	[-1.46; 0.56]
TBEP	No Detected	Ref	
	Detected	-1.92	[-5.09; 1.24]
TBP	Quartile 1	Ref	
	Quartile 2	1.17	[-2.31;4.65]
	Quartile 3	1.79	[-1.81;5.39]
	Quartile 4	-4.16	[-7.78;-0.55]
TCEP	<LOD	Ref	
	LOD-median	1.12	[-2.18; 4.42]
	>median	-1.01	[-4.21; 2.19]
T CPP*		-0.42	[-1.81; 0.98]
TDCPP*		-0.25	[-1.05; 0.54]
TEP*		-1.30	[-2.40; -0.19]
TMCP*		0.13	[-0.73;0.47]
TPP	Quartile 1	Ref	
	Quartile 2	6.21	[2.49;9.92]
	Quartile 3	3.61	[-0.09;7.32]
	Quartile 4	4.11	[0.27;7.95]

**log₂ transformed concentration*

Table S2. Association between OPFR postnatal exposure and score of PST, adjusted on OPFR prenatal exposure

OPFR		β	IC 95 %
EHDPP*		-1.23	[-2.19; -0.28]
TBEP	<LOD	Ref	
	LOD-median	-5.96	[-9.63; -2.29]
	>median	-4.04	[-8.13; 0.05]
TBP*		0.04	[-2.96; 3.04]
TCEP	<LOD	Ref	
	LOD-median	0.37	[-3.46; 4.20]
	>median	-4.47	[-8.52; -0.43]
T CPP	<LOD	Ref	
	LOD-median	3.64	[-0.07; 7.35]
	>median	-1.43	[-5.34; 2.48]
TDCPP*		-1.09	[-1.98; -0.19]
TEP	<LOD	Ref	
	LOD-median	0.43	[-3.45; 4.30]
	>median	2.90	[-1.31; 7.11]
TMCP	No Detected	Ref	
	Detected	-2.25	[-5.56; 1.05]
TPP	Quartile 1	Ref	
	Quartile 2	-4.94	[-9.39; -0.49]
	Quartile 3	-2.67	[-7.06; 1.73]
	Quartile 4	-8.67	[-12.81; -4.53]

**log₂ transformed concentration*

Titre : Exposition aux retardateurs de flammes organophosphorés et neurodéveloppement de l'enfant

Mots clés : retardateurs de flamme, exposition, environnement, périnatalité, cognition

Résumé : Les retardateurs de flamme organophosphorés (RFOP) sont utilisés principalement en remplacement de certains retardateurs de flammes bromés interdits depuis le début des années 2000. Les RFOP ont été retrouvés de manière ubiquitaire dans les environnements extérieurs et intérieurs mais l'exposition de la population, ses déterminants et ses effets possibles néfastes sur la santé, en particulier des jeunes enfants, n'ont été que peu étudiés, et jamais en France.

Les objectifs de cette thèse étaient d'estimer les expositions pré- et post-natales des enfants nés en France en 2011, d'identifier leurs déterminants et d'étudier leurs effets sur le neurodéveloppement à 3.5 ans grâce à la cohorte mère-enfant Elfe.

Nous avons estimé l'exposition pré- et post-natale des enfants pour 9 RFOP grâce aux concentrations mesurées dans les cheveux maternels à la naissance et chez l'enfant à 3,5 ans. Les prévalences d'exposition étaient > à 60% pour 6 RFOP ; le tris(1-chloro-2-propyl)

phosphate était retrouvé aux plus fortes concentrations chez les mamans et les enfants. L'IMC pré-grossesse, la réalisation de travaux de rénovation et l'exposition prénatale aux BDE 209 et BDE 47 étaient les déterminants majeurs de l'exposition prénatale alors que pour la période postnatale les déterminants majeurs étaient le revenu mensuel, le niveau d'étude de la maman et l'exposition prénatale au BDE 47. Enfin, plusieurs associations significatives ont été observées entre les expositions pré- et postnatales des enfants et le développement cognitif non verbal à 3.5 ans. Une diminution des capacités cognitives non verbales de l'enfant était associée à une augmentation de l'exposition prénatale à 2 RFOP (tri-n-butyl phosphate et triphenyl phosphate) et à une augmentation de l'exposition postnatale à 5 RFOP (ethylhexyl diphenyl phosphate, tris(2-butoxyethyl) phosphate, tris(2-chloroethyl) phosphate, tris(1,3-dichloro-2-propyl) phosphate et triphenyl phosphate).

Title : Exposure to organophosphorus flame retardant and child neurodevelopment

Keywords : flame retardants, exposure, environment, perinatal, cognition

Abstract: Organophosphate flame retardants (OPFR) are mainly used to replace certain brominated flame retardants that have been banned since the early 2000s. OPFR have been found ubiquitously in outdoor and indoor environments, but population exposure, its determinants and possible adverse health effects, especially for young children, have been little studied, and never been in France.

The objectives of this thesis were to estimate the pre- and post-natal exposures of children born in France in 2011, to identify their determinants and to study their effects on neurodevelopment at 3.5 years of age using the Elfe mother-child cohort. We estimated the pre- and post-natal exposure of children to 9 OPFR using concentrations measured in the maternal hair at birth and in the child at 3.5 years. Exposure prevalences were > 60% for 6 OPFR; tris(1-chloro-2-propyl) phosphate was found at the highest

concentrations in and children. Pre-pregnancy BMI, renovation work and prenatal exposure to BDE 209 and to BDE 47 were the major determinants of prenatal exposure, whereas for the postnatal period the major determinants were monthly income, the mother's level of education and prenatal exposure to BDE 47. Finally, several significant associations were observed between the children's pre- and post-natal exposures and non-verbal cognitive development at 3.5 years. A decrease in the child's non-verbal cognitive abilities was associated with an increase in prenatal exposure to 2 OPFR (tri-n-butyl phosphate and triphenyl phosphate) and with an increase in postnatal exposure to 5 OPFR (ethylhexyl diphenyl phosphate, tris(2-butoxyethyl) phosphate, tris(2-chloroethyl) phosphate, tris(1,3-dichloro-2-propyl) phosphate et triphenyl phosphate).