Sources, exposure and health risk to legacy and emerging Flame retardants in Spanish indoor environments. An integrated Health RISK Approach

2018-2022

Flame retardants

Flame retardants (FRs) are chemicals that prevent and / or delay the spread of a FIRE.

FRs are present in plastics, furniture, textiles, coatings, etc.

High temperatures
Abrasion
Cleaning

lead to volatilize, and to accumulate in AIR and DUST.

People can INHALATE, DERMAL UPTAKE, and INGEST flame retardants.

Some legacy FRs are banned or restricted because of HEALTH CONCERN

PBDEs
Polybrominates diphenil ethers

Dec
Dechlorans

HBCDD
Hexabromociclododecans

Neurodevelopment
Behavior
Reproduction

Emergy FRs replaced them as presumably safer and less persistent.

OPFRs
Organophosphates

NBFRs
Novel Brominated

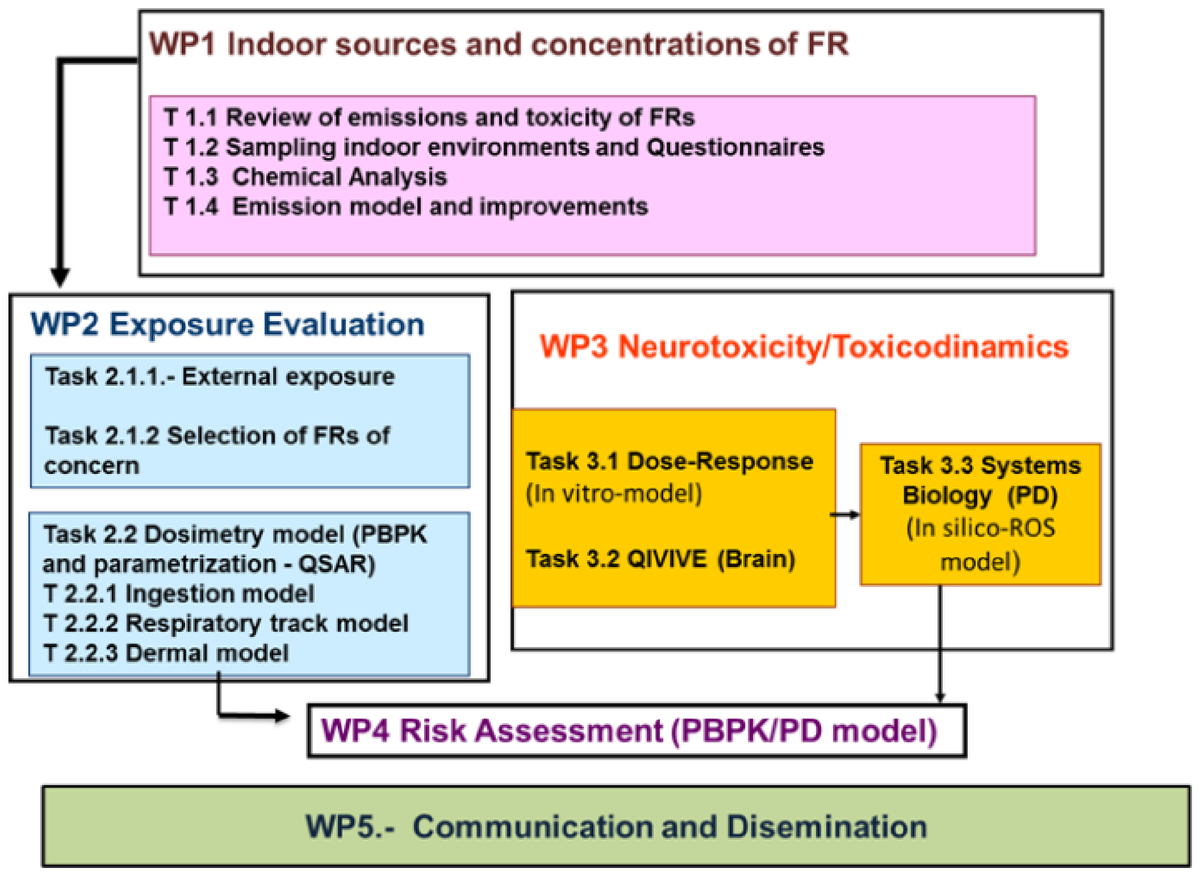
Aim

The aim of **FlameRISK project** is to understand how and to what **extent FRs are released from consumer products** in Spanish indoor environments and to assess the **human exposure** and the associated **health risks**.

Specific objectives:

- Objective 1: To identify and quantify ” presence of flame retardants (FRs) (WP1)
- Objective 2: To evaluate the “indoor” exposure of FRs (WP1)
- Objective 3: To predict indoor concentrations considering FRs emissions due to their migration capacity (WP1)
- Objective 4: To get a ranking of the most used FRs (WP1)
- Objective 5: To evaluate the internal and external exposure of FRs in indoor environments for the population of Spain (WP2)
- Objective 6: To develop a pharmacodynamic model capable of assessing the risk of neurotoxicity due to FRs (WP3)
- Objective 7: To obtain a parameterization of the “in silico” model applied to the pharmacodynamic model of WP2 that allows to evaluate the risk of neurotoxicity by ROS in brains exposed to FRs (WP3)
- Objective 8: To develop a dose-response curve of in vitro ROS levels caused by FRs (WP3)
- Objective 9: To construct an Integrative Toxicological System (model) to predict adverse effects (neurotoxicity) by exposure to FRs in humans (WP4)
- Objective 10: To disseminate the results (WP5)

Workpackages and tasks



Research team

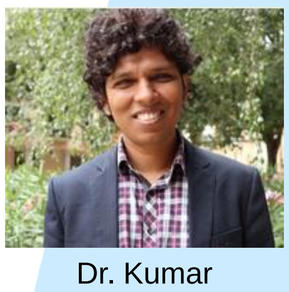
Dr. Schuhmacher

Dr. Rovira

Dr. Esplugas

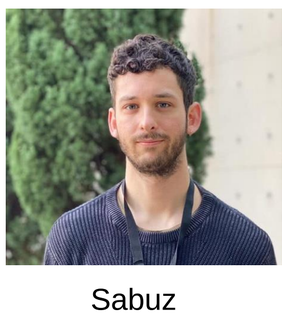
Dr. JL Domingo

Dr. Mari



Dr. Kumar

Deepika



Sabuz

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Collaborations

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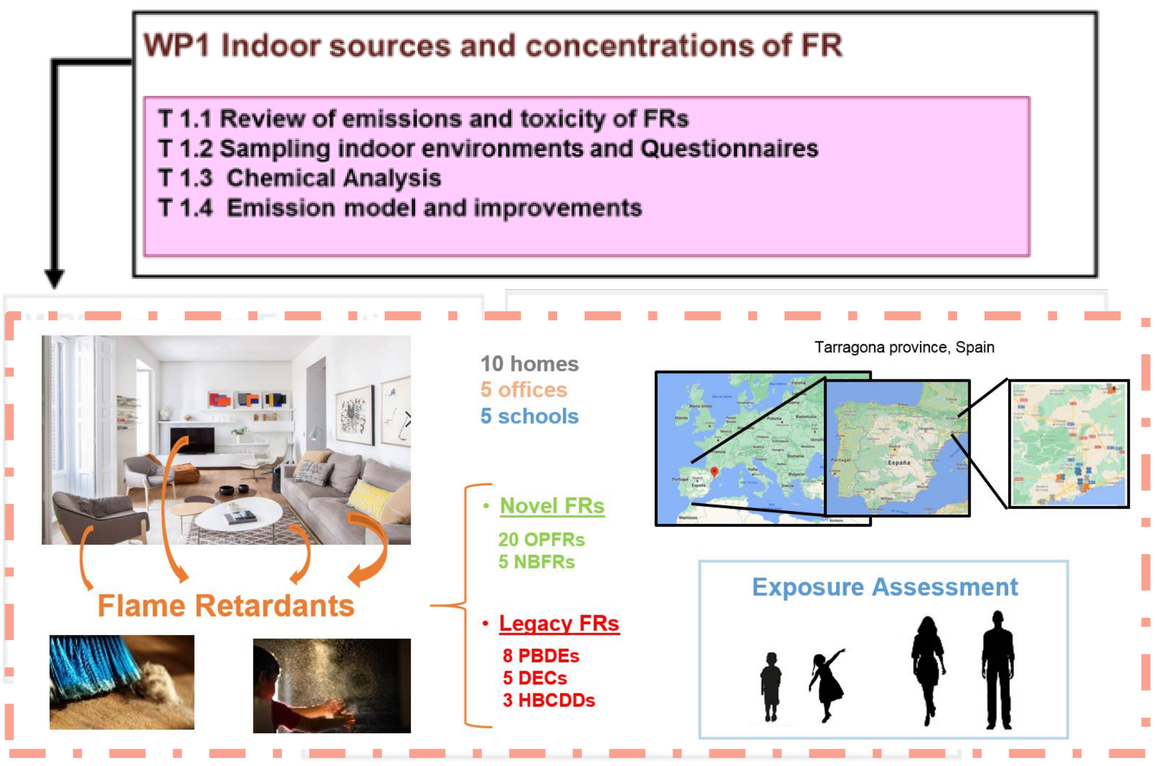
WP1



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journal homepage: www.elsevier.com/locate/scitotenv

Emerging and legacy flame retardants in indoor air and dust samples of Tarragona Province (Catalonia, Spain)

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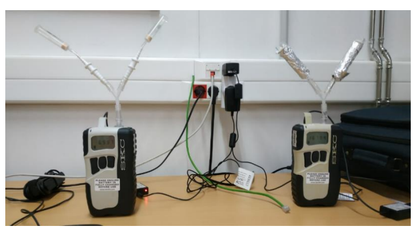
Esplugas et al., 2022. DOI: 10.1016/j.scitotenv.2021.150494.

The study was aimed at 1) identifying and quantifying the indoor levels of 41 FRs in Tarragona Province (Catalonia, Spain), 2) to study differences among houses, offices and schools, 3) to identify FR profiles and sources, and 4) to assess human exposure to FR and the associated health risks.

- **41 FRs** were selected for the study:
  - **16 legacy FRs** (8 PBDEs, 3 HBCDDs and 5 DECs)
  - **25 novel FRs** (20 OPFRs and 5 NBFRs)
- Samples from **air** and **settled dust** of 20 indoor Spanish environments (10 homes, 5 offices and 5 schools) were collected.
- FR from samples were extracted and measured by chromatography techniques.
- For human health risk assessment of FRs, we calculated the:
  - **Exposure** through air **inhalation** and dust **ingestion** for adult and children
  - **Non-carcinogenic** and **carcinogenic risks** considering the total exposure



Air (during 24h)

Dust

TFC combinated with MS-MS

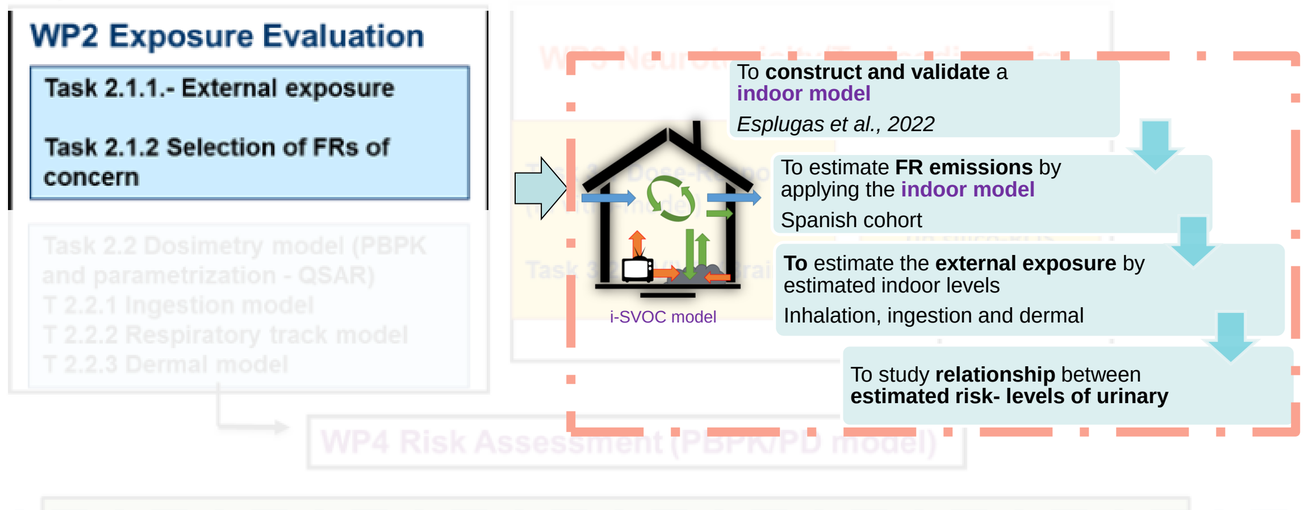
GC-MS-MS

idaea CSIC

- ✓ We confirmed the **presence** of almost all measured FRs in **air and dust**.
- ✓ First time in Europe to confirm the presence of **TEP, TCIPP, T2IPPP, TPPO, DCP, TMCP i B4IPPPP** in **air**.
- ✓ Variability in associations FR-environmental profiles.
- ✓ Variability in differences between levels among homes, schools and offices.
- ✓ The current **risk assessment** suggests that exposure to FRs was **below** the assumable health risks (hazardous quotient and cancer risk below 1 and 10^{-6}, respectively).

WP2

The study was aimed at 1) modeling and validating the distribution of TPhP and TCPP in indoor Spanish environments (air and dust of homes, offices and schools), 2) estimating the emissions of TPhP and TCPP from devices, 3) calculating the risk assessment derived from estimated emissions, and 4) studying relationships between estimated health risk and urine metabolites.



- ✓ **Ability** of **indoor model** (is-VOC) to **estimate** levels in air and dust of both **TClPP** and **TPhP**.
- ✓ **Estimated levels** of both FRs for the Spanish **Cohort** (GENEIDA) were even more **similar** of experimental ones than validation results.
- ✓ The assessment of **estimated exposure** showed levels for the toddlers **similar** than those described by **literature**.
- ✓ Risk assessment based on estimated exposure for both TClPP and TPhP did **not** showed **non-carcinogenic risk** for toddlers of the cohort.
- ✓ Variability among characteristics of environments and levels of urinary metabolites lead to a lack of correlation between estimated exposure and metabolite levels.

- **Two OPFR** were slected for the study:
  - tris(chloroisopropyl)-phosphate (**TCPP**)
  - triphenyl phosphate (**TPhP**)
- Concentrations of TCPP and TPhP were **modeled** in Spanish indoor environments (schools, office and homes).
  - Model was constructed using **i-SVOC software**. Building parameters (i.e.: room volume and ventilation) and FR sources (i.e., electronic devices) were introduced from existing data (Esplugas et al. 2022).
  - **Four scenarios** were run, considering high and low **ventilation**, as well as high and mid **emissions factors**.
- Model was **validated** considering previously measured indoor air and dust samples for both FRs (Esplugas et al. 2022).
- **Emissions** of TCPP and TPhP from devices were **estimated** in a **Spanish cohort** (Andalusia) for **toddlers** (12 and 24 months) by the model
  - Building parameters were introduced from collected data of indoor environments where toddlers lived.

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- For human health risk assessment of FRs, we calculated the:
  - **Exposure** through air **inhalation** and dust **ingestion** for adult and children
  - **Non-carcinogenic risk** considering the total exposure
- Correlations between health risk and urine metabolite **(DPhP and DCPP)** in the same cohort were studied.

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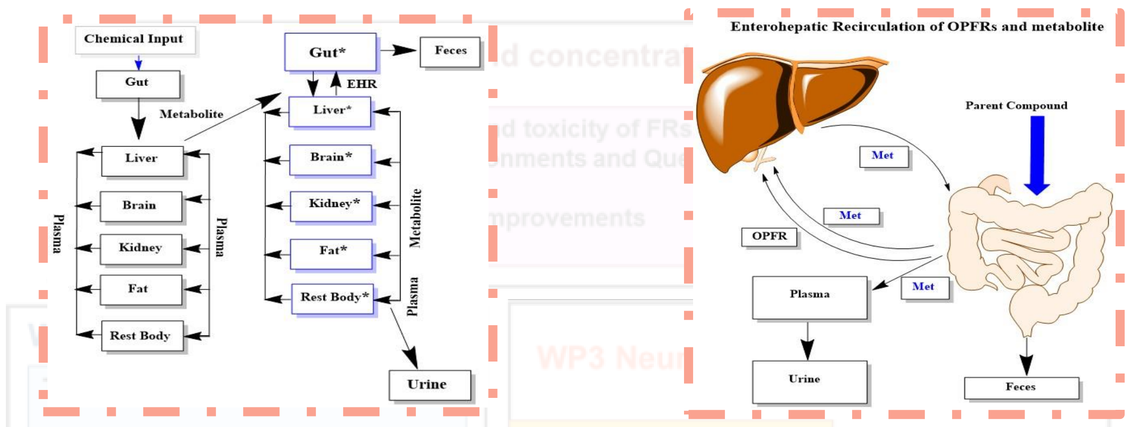
WP2



Task 2.2 Dosimetry model (PBPK and parametrization - QSAR)
T 2.2.1 Ingestion model
T 2.2.2 Respiratory track model
T 2.2.3 Dermal model

The objective of this work was to **develop** and **validate PBPK Model** for **three OPFRs** in **rat** and **further extrapolate it to human**

- A **six compartment PBPK Model** for OPFRs (**TDCPP**, **TCPP** and **TCEP**) along with major metabolite (BDCIPP, BCIPP and BCEP) was developed.
  - In the model, chemical exchange between blood and several organs was restricted by blood flow also called as perfusion limited model.
  - Data available from the literature was taken for validating the model in male Wistar rats.
  - Several parameters were calculated while others were optimized based on Markov Chain Monte Carlo simulation.
- After initial optimization, **parameters** were further **refined** based on visual fitting.
- **Sensitivity analysis** was conducted for the model to find the parameters affecting the output.

✓ All the OPFRs have longer half-life with chemical being detected for 168 hour after single administration compared to short acting chemicals like BPA.

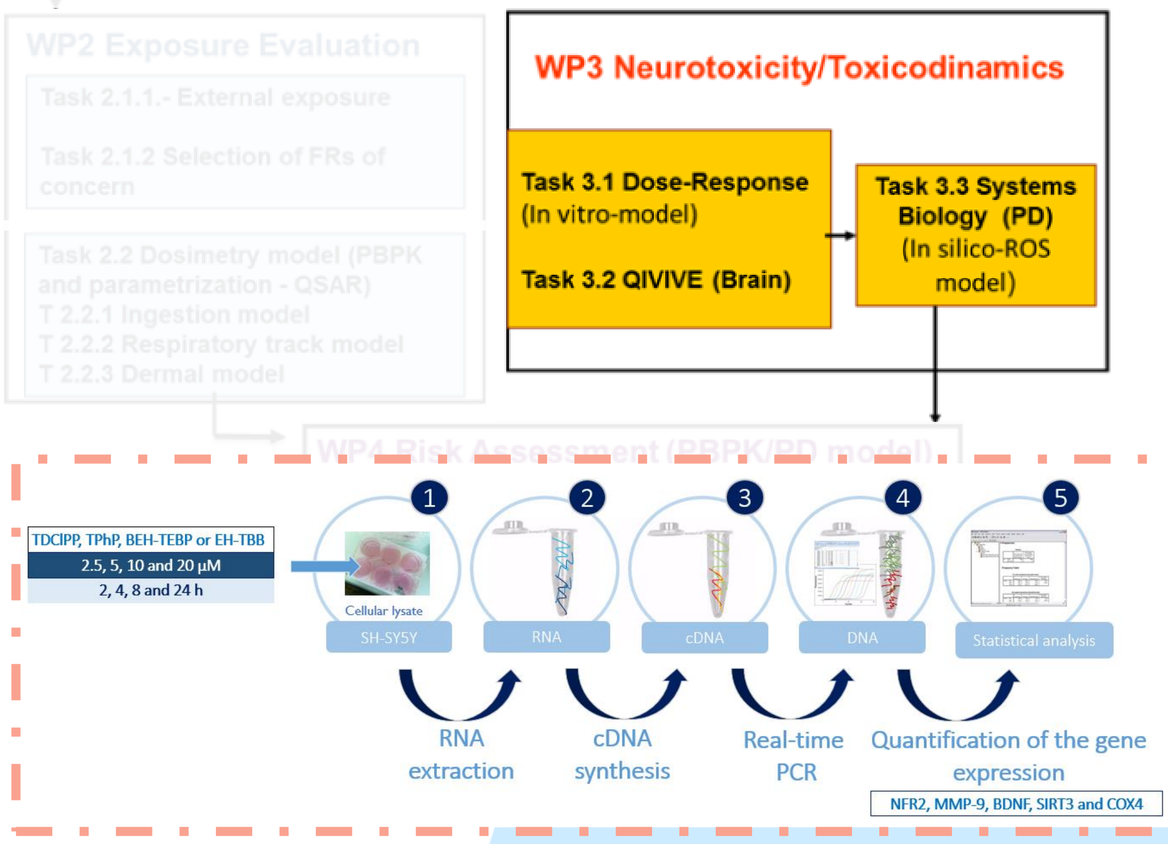
✓ Distribution of OPFRs was **high in kidney and liver** whereas in case of brain tissue, the elimination is quite slow suggesting their ability to affect brain.

✓ Generic PBPK model **can be developed for all OPFRs** since similar kind of toxicokinetic is observed in all three chemicals.

✓ This model can serve as starting point for **further extrapolation** to humans for risk assessment.

WP3

The present study was aimed at assessing the in vitro acute neurotoxicity potential of two OPFRs (TDClPP and TPhP) and two NBFRs (BEH-TEBP and EH-TBB).



- SH-SY5Y cells were exposed to 4 EFRs (**TDClPP**, **TPhP**, **BEH-TEBP** or **EH-TBB**) or control (DMSO 0.5%) at doses ranging **2.5-20 µM** during **2-24h**.
- Cell **viability** was assessed by MTT assay
- **Intracellular ATP** was quantified by luminescence technique
- Cells were lysed and RNA was further extracted to study the gene expression by RT-PCR of: Cytochrome c oxidase subunit 4 (**COX-4**), Sirtuin 3 (**SIRT3**), nuclear factor erythroid 2-related factor 2 (**NRF2**), Matrix Metallopeptidase 9 (**MMP-9**) and Brain Derived Neurotrophic Factor (**BDNF**), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH, control).
- Supernatant was collected to measure the release of cytokines tumor necrosis factor **(TNF)-α**, interleukin **(IL)-6**, **IL-1B** and **IL-10**
- All end-points were useful to determinate mitochondrial function, oxidative stress, inflammatory response as well as neural plasticity and development

✓ **Selected EFRs** (TDClPP, TPhP, EH-TBB and BEH-TBP) did **not impair neural function** on SH-SY5Y as acute response at the selected doses on

- ✓ **Viability** after 24 h
- ✓ **Oxidative stress** assessed by the expression of Nrf2 at selected doses (2.5, 5, 10 and 20 µM) and time-points (2, 4, 8 and 24 h)
- ✓ **Mitochondrial function** by the expression of COX4 and SIRT3 and intracellular **ATP** levels at selected doses for 2- 24 h. **OPFRs** showed a **little decrease on ATP** of about 20% which was not statistical significant vs control.
- ✓ **Neural development** and **plasticity** (expression of both MMP-9 and BDNF genes) at selected doses and time-points

✓ **Lower potential of EFRs** in neural affection **in comparison to legacy FRs**, because legacy FRs are described to affect these endpoints at same even lower doses,

✓ **First study** focused to evaluate the affection of the **two NBFR** (EH-TBB and BEH-TBP) on neural cells as well as of **TPhP** on SH-SY5Y.

✓ **First time** to determinate the selected **endpoints** after **FR exposure** on **neural cells**.

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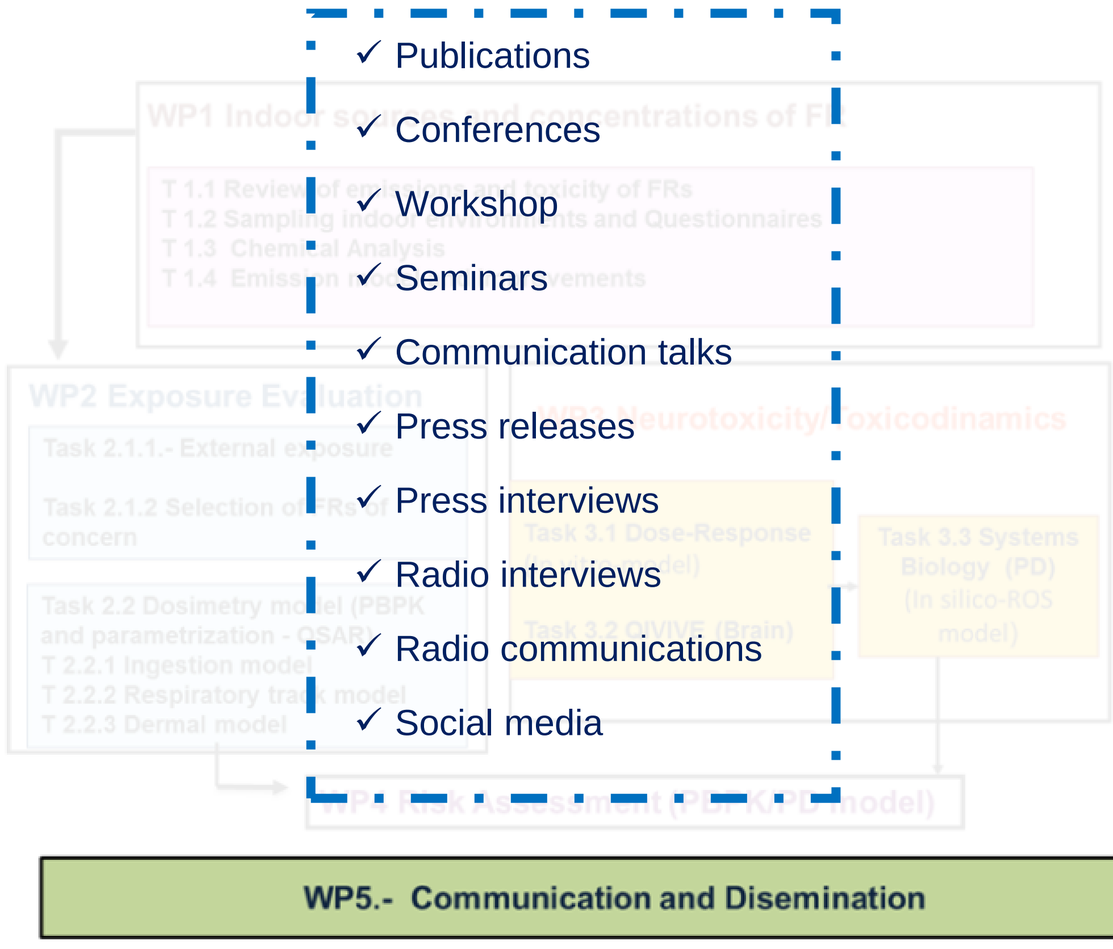


Dissemination

Publications

Esplugas, R., Rovira, J., Mari, M., Fernández-Arribas, J., Eljarrat, E., Domingo, J.L., Schuhmacher, M., 2022. **Emerging and legacy flame retardants in indoor air and dust samples of Tarragona Province (Catalonia, Spain)**. Sci. Total Environ. 806, 150494. https://doi.org/10.1016/J.SCITOTENV.2021.150494

Sabuz Vidal, Ó., Deepika, D., Schuhmacher, M., Kumar, V. 2021. **EDC-induced mechanisms of immunotoxicity: a systematic review**. Critical Reviews in Toxicology., 51(7), 634–652. https://doi.org/10.1080/10408444.2021.2009438

Esplugas, R., Linares, V., Bellés, M., Domingo, J.L., Schuhmacher, M., 2022. **In vitro neurotoxic potential of emerging flame retardants on neuroblastoma cells**. *submitted*

Esplugas, R., Rovira, J., García, H., Kumar, V., Mari, M., Hernández, A.F., Lacasaña-Navarro M., Domingo, J.L., Schuhmacher, M. 2022. **Estimated exposure of flame-retardants in Spanish toddlers: a modelling approach**. *submitted*

Conferences

CSIC NOVENA JORNADA: MEDI AMBIENT I SOCIETAT: PAUTES PER A LA GESTIÓ AMBIENTAL 5 (Barcelona) 5 June 2019
FlameRISK project, Dr Schuhmacher

SETAC LATINO AMERICA (Cartagena de Indias, Colómbia) 15-18 Sep 2019
FlameRISK: sources, exposure and health risk to legacy and emerging Flame retardants in Spanish indoor environments. An integrated health RISK approach, Dr Schuhmacher

INTERRREG CENTRAL EUROPE InAir Q. International Conference on Integrated Problem-Solving Approaches to Ensure School children's Health (Budapest, Hungría) 23-24 May 2019
Sources, exposure and health risk to legacy and emerging Flame retardants in Spanish indoor environments. An integrated health RISK approach (FlameRISK), Dr Rovira

SETAC Europe 32nd Annual Meeting (Copenhagen, Denmark) 15-19 May 2022
Indoor concentrations of flame-retardants in Spanish environments: a multimedia modelling approach, Dr Rovira

Physiologically Based Pharmacokinetic Model (PBPK) for 3 flame retardants (TDCIPP, TCIPP, TCEP) in animals and extrapolation to human for risk assessment, Dr Schuhmacher

In vitro neurotoxic effects of emerging flame retardants at non-cytotoxic concentrations on neuroblastoma cells, Dr Schuhmacher

International Union of Toxicology (IUTOX) conference (Masstrich, Netherland) 18-21 Sep 2022
Evaluation of the generic Physiologically Based Pharmacokinetic Model (PBPK) for organophosphate flame retardant (OPFRs) and neurotoxic risk assessment in children, Deepika

Workshop

1 Jornadas sobre CONTAMINACIÓN POR PLÁSTICOS: Retos científicos, empresariales y legislativos (PLASTIC'2020) (Barcelona) oct 2020,
Air and dust indoor concentrations of flame retardants in Spanish environments, Dr Esplugas

Communication

Communication talks

Xerrades Divulgatives de Ciència enmarcada en la Nit Europea dels Investigadors (Tarragona) 27 nov 2020
L'aire que respirem a casa pot afectar el cervell?, Dr Esplugas

Xerrada 100tifiques. **És segur l'aire que respirem a casa?**, Dr Esplugas
- IES Vidal Barraquer 25 Nov 20
- IES Vilassar de Mar 11 Feb 21

Visites IES, NEXES program of URV. **És segur l'aire que respirem a casa?**, Dr Esplugas
- Institut Camarles (Camarles) 13 Oct 20
- La Salle de Reus (Reus) 02 Nov 20
- INS Sòl de Riu (Alcanar) 16 Nov 20
- IES Narcís Oller (Valls) 18 Jan 2022

Press releases

El centre de recerca TecnATox mesurarà la contaminació dels retardants de flama a llars, oficines i escoles URVActiv@ 3 July 19

Un estudi detecta la presència de retardants de flama a dins de cases, oficines i escoles URVActiv@ 25 Oct 21

** Press release was further disseminated in other 18 journals*

Press interview

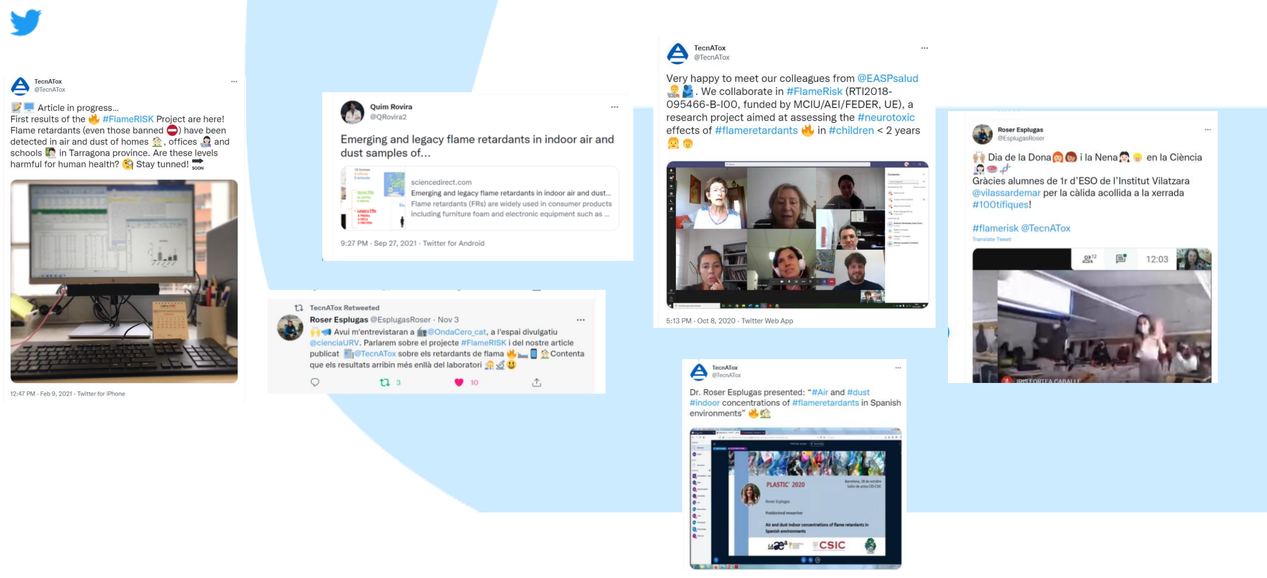
Fet a Tarragona Sep-Oct (pages 64-65)
És segur l'aire que respirem a casa?, Dr Esplugas

Radio interviews

Onda Cero, Dr Esplugas 3 Nov 21
Radionacional, Dr Esplugas 15 Dec 21

Radio communication

Radionacional 04 Jan 22



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