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Doctoral thesis:

Functional outcomes of flame retardant action in immune cells

Praca doktorska:

Funkcjonalne konsekwencje działania opóźniaczy palenia w komórkach układu odpornościowego

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Education

2021-2025	**Ph.D. in immunology**, Institute of Medical Biology, Polish Academy of Sciences, Supervisor: Prof. Lukasz Pulaski **Thesis Title: Functional outcomes of flame retardant action in immune cells**
2015-2018	**M.Sc. in immunology**, Iran university of Medical Science **Thesis Title: Comparison of the frequency of B1 and NK cells in the peripheral blood, also** **IL-6 and IL-10 in serum between multiple sclerosis and neuromyelitis optica patients** **Supervisors: Jazayeri, Mir Hadi**
2011-2015	**B.Sc. in cellular and molecular biology**, University of Isfahan

Achievements

List of publications/manuscripts included in the doctoral dissertation

Published papers

1. Cellular and physiological mechanisms of halogenated and organophosphorus flame retardant toxicity. **Leila Khani,** Leonardo Martins, Łukasz Pułaski. Science of the Total Environment. 2023, 897:165272.

   IF_{2023} = 8.2, pkt. MEiN = 200, citation: 30

2. Tetrabromobisphenol A, but not bisphenol A, disrupts plasma membrane homeostasis in myeloid cell models–A novel threat from an established persistent organic pollutant, **Leila Khani**, Maciej Studzian, Leonardo Martins, Michał Gorzkiewicz, Łukasz Pułaski, Science of the Total Environment. 2025, 961:178284.

   IF_{2025} = 8.0, pkt. MEiN = 200, citation: 2

Manuscripts accepted for review

3. TBEP and TCP impair metabolic and immune functions in human macrophages: a novel redox-related activity with potential immunotoxic consequences, **Leila Khani**, Maciej Studzian, Leonardo Martins, Łukasz Pułaski, submitted to Environment International in July 2025.

   IF_{2025} = 9.7, pkt. MEiN = 140

4. The brominated flame retardant DecaBDE inhibits low-density lipoprotein macropinocytosis in human M2 macrophages, **Leila Khani**, Maciej Studzian, Leonardo Martins, Łukasz Pułaski, submitted to Archives of Toxicology in July 2025.

IF_{2025} = 6.9, pkt. MEiN = 140

List of publications not included in the doctoral dissertation

5. The frequencies of peripheral blood CD5+ CD19+ B cells, CD3− CD16+ CD56+ NK, and CD3+ CD56+ NKT cells and serum interleukin-10 in patients with multiple sclerosis and neuromyelitis optica spectrum disorder, **Leila Khani**, Mir Hadi Jazayeri, Reza Nedaeinia, Mahmood Bozorgmehr, Seyed Masood Nabavi, Gordon A Ferns, Allergy, Asthma & Clinical Immunology. 2022; 18(1):5.
6. Comparison of OX40 expression in patients with multiple sclerosis and neuromyelitis optica as an approach to diagnosis, Mostafa Manian, Morteza Motallebnezhad, Reza Nedaeinia, Rasoul Salehi, **Leila Khani**, Gordon A Ferns, Mir Hadi Jazayeri, Allergy, Asthma & Clinical Immunology. 2023; 19(1):19.
7. Crosstalk between non-coding RNAs expression profile, drug resistance and immune response in breast cancer, Seyed Ali Miraghe, Nasim Ebrahimi, **Leila Khani**, Atena Mansouri, Asieh Jafarzadeh, Amirhossein Ahmadi, Amir Reza Aref, Pharmacological Research. 2022; 176:106041.
8. Targeting the metabolism of cancer stem cells by energy disruptor molecules, Tahere Dadgar, Nasim Ebrahimi, Amir Reza Gholipour, Maryam Akbari, **Leila Khani**, Amirhossein Ahmadi, Michael R Hamblin, Critical Reviews in Oncology/Hematology. 2022; 169:103545.
9. Attribution of ghrelin to cancer; attempts to unravel an apparent controversy, Saeed Soleyman-Jahi, Fatemeh Sadeghi, Amin Pastaki Khoshbin, **Leila Khani**, Venus Roost, Kazem Zendehdel, Frontiers in Oncology. 2019; 9:1014.
10. Gold nanoparticle and polyethylene glycol in neural regeneration in the treatment of neurodegenerative diseases, Tayebe Aghaie, Mir Hadi Jazayeri, Mostafa Manian, **Leila Khani**, Marjan Erfani, Majid Rezayi, Gordon A Ferns, Amir Avan, Journal of Cellular Biochemistry. 2019; 120(3):2749-55.

Conference and poster presentations:

1. Cytokines and KAI 2024, October 20-23 2024, Seoul, South Korea, Immunotoxic effects of organophosphate flame retardants on pro-inflammatory innate immune responses in monocytes and macrophages
2. FEBS-EMBO course on Lipids, Proteins and their Interactions in Organelle Biology, 29 May-4 June 2022, Greece, Plasma membrane lipid organization is disrupted in monocyte-macrophage models by hydrophobic flame retardants.
3. SETAC Europe 32nd Annual Meeting, May 2022 Copenhagen, Differential impact of brominated and organophosphate flame retardant POPs on gene expression in monocyte-macrophage differentiation models.

International research visits:

- Research visit at University of Cambridge about profiling lipidomic profile of Epstein-Barr virus transformed-B lymphocyte, six months, April to September 2023.
- Research visit at ETH, Zurich, about developing nanobodies to block liver metastasis in colorectal cancer, six months, April to September 2025.

Distinctions and awards:

- Mobility 6-month STER NAWA research fellowship (2025), funded by NAWA and granted by the University of Lodz
- 12-month STER NAWA incentive scholarship (2024–2025), funded by NAWA and granted by the University of Lodz
- Audience award and third place in the 3-minute science talk competition, University of Lodz and Medical University of Lodz (2024)

Organizational activity

- Member of the International Student Committee, University of Lodz (2024–2025)

Introduction

Flame retardants as environmental hazards

Flame retardants (FRs) are widely incorporated into consumer and industrial products, for example furniture, textiles, building materials, and electronic devices, to reduce flammability. Many FRs are complex organic molecules with halogen and/or phosphorus groups and they resist biotransformation, leading to environmental persistence and bioaccumulation; as a result, many are classified as persistent organic pollutants (POPs). These chemicals are not biologically inert, and their exposure can produce direct and indirect effects on organisms and ecosystems (1).

Special attention should be given to the public health hazards of FRs. Epidemiological and clinical studies showed that FR exposure can lead to endocrine dysfunction, reproductive and neurodevelopmental disorders, carcinogenesis, metabolic dysregulation, and immune dysfunction (2). Structurally, most FRs can be grouped into brominated flame retardants (BFRs), organophosphate flame retardants (OFRs), and halogenated organophosphates (3). Regulatory restrictions on legacy BFRs have driven a shift toward OFRs, yet evidence for deleterious effects of this substitution is emerging as newer compounds also show persistence, bioaccumulation, and toxicity (9). Real world exposures often involve complex mixtures, and additive or synergistic effects remain a major challenge for risk assessment (10).

Immune system as a target for FRs

The immune system, consisting of adaptive and innate immunity, maintains host homeostasis by detecting and eliminating pathogens, supporting tissue repair, and maintaining immune tolerance. Immunotoxicological studies showed that some FRs dysregulate both humoral and cellular adaptive

immunity. Innate immunity is the first line of defense and if necessary, shapes adaptive responses. Innate cells rapidly trigger cytokine and chemokine release, generation of reactive oxygen species (ROS) and reactive nitrogen species, complement activation, and phagocytosis through pattern recognition receptor such as Toll-like receptors (TLRs) and NOD-like receptors (17). Neutrophils, macrophages (MQs), dendritic cells (DCs), and natural killer cells coordinate these responses to set the inflammatory milieu for antigen presentation and lymphocyte priming (18). These processes depend on signaling thresholds, membrane architecture, receptor trafficking, and cellular energy, and FRs that perturb them can impair effector function (19).

MQs as immunotoxicity and immunomodulation targets

MQs are professional phagocytes distributed in the circulation and peripheral tissues. They perform phagocytosis, regulate the initiation and resolution of inflammation, present antigen to T cells, and support tissue repair and remodeling (23, 24). Exposure to environmental xenobiotics can compromise these functions by altering plasma-membrane organization, receptor trafficking, modulating transcriptional pathways, and perturbing cellular metabolism and redox balance (25-29). These changes shift signaling thresholds and effector responses and can lead to failure of pathogen killing and resolution of inflammation, as well as dysregulation of immune responses that ultimately increase infection risk, contribute to chronic inflammatory and autoimmune disease, reduce vaccine responsiveness, and weaken anti-tumor surveillance (30, 31).

Immunomodulatory xenobiotics target membrane properties and effector functions in MQs

The biophysical properties of the plasma membrane, including its order, polarity, rotational and lateral mobilities, cholesterol content, microdomain organization, curvature, and tension, control cellular effector functions, including receptor nanoclustering, adaptor recruitment, endocytic pit formation, and vesicle fusion. In MQs, these parameters affect clustering of key receptors like FcεRI, FcγR, and TLRs and regulate activation and uptake thresholds for signaling pathways such as NF-κB, MAPK, and interferon regulatory factor (26, 32-39). Observations support a general model in which membranes are early and important targets of FRs, potentially also in MQs. Direct partitioning and indirect metabolic modulation can jointly reshape membrane biophysics and composition, with downstream consequences for signalling, trafficking, and cell functions.

Membrane trafficking modulators impact the function of MQs

Membrane trafficking in MQs regulates pinocytosis, phagocytosis, and receptor mediated endocytosis, thereby controlling cargo internalization, receptor turnover, and antigen presentation (46-48). MQs can be divided into different subtypes, the main ones being M1 and M2, which are known for their pro-inflammatory and modulatory phenotypes, respectively. M2 MQs support tissue repair and can become foam cells by internalizing lipids, which is a key phenotype in atherosclerosis (49). Lipid uptake occurs via scavenger receptors such as SR-A, CD36, and LOX1 through receptor-mediated endocytosis (50), with macropinocytosis contributing substantially to lipoprotein uptake (51). In addition, phagocytosis of apoptotic cells and aggregated LDL can also contribute to foam cell formation (52). Together these routes

promote lipid accumulation, reprogram signaling and metabolism, and reinforce a storage phenotype of MQs.

Redox homeostasis disruption impairs MQ function

Redox homeostasis in MQs requires controlled ROS generation and removal to sustain pathogen killing and redox-sensitive signalling and at the same time avoid cellular component damage. The oxidative burst depends on NADPH, with NOX2 at plasma and phagosomal membranes reducing oxygen to superoxide and hydrogen peroxide (66); additional ROS originate from mitochondrial complexes I and III and other enzymes including xanthine oxidoreductase, uncoupled nitric oxide synthase, peroxisomal oxidases, endoplasmic reticulum oxidoreductases, and cytochrome P450 cycling (67-70). Suppression or mislocalization of ROS can suppress pathogen killing function of MQs (71-73). FRs can perturb redox maintenance in myeloid cells.

Research aims and hypothesis

Human exposure to FRs is unavoidable. Regretfully, their hazardous effects on public health have not been elucidated enough. Current studies focus mainly on endocrine and neurodevelopmental outcomes, whereas effects on the immune system remain underexplored. We decided that preliminary literature research is necessary to correctly formulate the goals of the experimental part of doctoral thesis. A comprehensive review was therefore the first step to map exposure sources across major chemical classes, evaluate methodological limitations, and outline plausible biological mechanisms linking exposure to disease. The aim of this review was to assist and guide us in choosing the relevant FRs, their concentrations and formulations for application. It was also needed for selecting appropriate cellular targets, laboratory models and methodologies, as well as experimental endpoints and conditions that would be informative with regard to the overall goal of filling the knowledge gap about FR immunotoxicity.

Within the toxicological landscape of FR action, immunity as a neglected target provides a broad scope for experimental investigations. Within my doctoral thesis, we decided to focus on human myeloid cells as crucial effectors of innate immunity, and more specifically on MQs as multi-role cells whose functions directly determine infection control, tissue repair, and inflammatory disease outcomes.

In order to narrow down the choice of FRs to study, we selected sixteen compounds (Table 1) so as to include representative compounds that were previously used or are currently used in large volumes across the world. In addition, we considered structural diversity, including both BFRs and OFRs with different level of lipophilicity.

An initial survey of the sixteen FRs in myeloid cell lines and *ex vivo* models of MQs yielded preliminary findings, which are not presented in this thesis but were used to formulate the experimental aims and hypotheses of our further laboratory research. These preliminary results included cytotoxicity testing in various cell types, as well as a range of biological endpoints related to immune function, metabolism, signalling and gene expression. It allowed us to:

- select the most bioactive FRs (as well as negative control FRs), their non-cytotoxic concentrations and exposure conditions to cover both short and longer exposures (short treatment captures rapid signalling and enzymatic effects, while long incubations allow transcription-dependent mechanisms to emerge);
- formulate specific research hypotheses related to potential immunomodulatory mechanisms which could disrupt MQ function.

Within our central research hypothesis, namely that **exposure to selected FRs can have a deleterious effect on the structural, signalling and functional elements of human MQs**, we were thus able to isolate the following individual phenomenological hypotheses:

1. Selected FRs can change the properties of biological membranes in MQs.

We expected hydrophobic FRs to change the biophysical properties of membranes, including molecular order, polarity, and mobility, potentially leading to modification of membrane-related immune functions.

2. Selected FRs can modify membrane trafficking functions in MQs.

We expected membrane-active FRs to modify membrane trafficking events, e.g. altering phagocytosis, receptor-mediated endocytosis, or pinocytosis.

3. Selected FRs can modify the redox homeostasis in MQs.

We expected some FRs to influence the balance of reactive oxidant production and elimination in MQs, potentially by modulating ROS sources, scavenging them directly or impacting endogenous antioxidants.

4. Selected FRs can affect the capacity of MQs to eliminate pathogens.

We expected FRs to alter uptake and clearance of pathogens (e.g. bacteria) in MQs by disrupting any of following cellular events: phagocytosis, phagosome maturation, and redox dependent killing.

In summary, the thesis aimed to fill the knowledge gap in immunotoxicology of FRs using a relevant panel of FR exposures in laboratory models of human MQs with mechanistically informative assays. The direct research goals were to: a) identify the FRs potentially most dangerous for human health via their immunotoxic action towards MQs; b) verify the extent of modulatory and deleterious effects of FR exposure on functional phenomena included in the phenomenological hypotheses listed above; c) explain the molecular and cellular mechanisms of identified phenomena, including the direct and indirect targets of FR action.

Research methodology

Our preliminary research allowed us to pre-select compounds of interest from among the full set of originally planned sixteen representative FRs. Viability/cytotoxicity assays made it possible to select exposure conditions (concentration, time) that would not be directly toxic to the cells, but would be bioactive and environmentally relevant (similar to conditions that can be encountered in actual in vivo

exposure). Confirmatory experimental data about cytotoxicity of individual FRs in the investigated cell models is included in the content of the thesis. In some assays, we needed to distinguish direct biochemical mechanisms from indirect ones that require regulatory genetic events, so we applied different exposure times for that purpose.

Since our hypotheses concerned elements of the human immune system (specifically, the monocyte-MQ differentiation axis), we applied commonly used laboratory models of the relevant cell type in such a way as to maximize the physiological relevance of obtained information, reproducibility of research material and the possibility of using research methods that require a large amount of input resources. Thus, we used a series of myeloid-origin cell lines which differ in the level of molecular and functional markers of MQ differentiation. We also used ex vivo isolated human monocytes (obtained from buffy coat collected from the local blood bank) which were in vitro differentiated to MQ phenotype. Finally, we also used these in vitro differentiated human MQs after subsequent polarization to one of the recognized phenotype subtypes: M1 or M2. This combined, structured approach allowed us to address such problems as uncertain physiological status of immortalized cell lines or donor to donor variability in blood samples.

In selecting the methodology (regarding the investigated endpoints and laboratory techniques), we used a complementary approach to methods addressing the same phenomena at different levels of organization. For molecular events and interactions, we used biophysical and biochemical techniques like e.g. solvatochromic or fluorogenic dyes; when subcellular events and processes were involved, we applied e.g. microscopy or gene expression analysis; for functional effects at the whole-cell level, dedicated measurements such as phagocytosis or bacterial killing assays were used. In this way, we sought to provide data which would allow us to draw toxicologically relevant conclusions that would point both to the overall outcomes of FR exposure in MQs and to the individual mechanisms that lead to those outcomes.

Discussion

The main question of my thesis is the immunomodulatory effect of FRs in human MQs. Although many studies address hazards of FRs for human health, including disruption of cell physiology, endocrine signaling, genome integrity, and reproduction, evidence for immune effects remains limited (89-92). Our literature review shed light on this understudied field. Many of the existing immunotoxicological studies are descriptive and often use cytotoxic and non-physiological concentrations of FRs in less directly relevant animal models like zebrafish, chicken, rats, or immortalized cell lines such as THP-1, which may differ functionally and phenotypically from primary human MQs (2, 56, 93).

With regard to mechanistic studies of FR action, the few studies that concerned themselves with membrane biophysics investigated only one of the biophysical properties, limited to the plasma membrane, and overinterpreted the results as pertaining to inadequately-defined “fluidity” (42). To address this simplification, our study included a complementary methodology of studying acyl chain order, lateral and rotational diffusion, and polarity in both plasma and internal membranes. Inclusion of BPA as a

non-brominated control for TBBPA demonstrated the contribution of bromination at the molecular level in TBBPA partitioning into membrane and highlighted the importance of an appropriate control (41, 42, 94).

Pinocytosis is a membrane-dependent uptake process present in many cell types, including cancer cells which use it for nutrient acquisition or DCs where it is the route of internalization of soluble antigens (95, 96). Some viruses also exploit this route to enter host cells (97). In all above-cited studies, pinocytosis was defined by measuring dextran uptake, a non-physiological cargo. In MQs, native LDL can enter the cells via macropinocytosis regulated by an MQ-specific PI3Kγ/Akt3/WNK1/SGK1/Cdc42 signaling axis (53). Our study focused on human M2 MQs, a subtype central to foam cell formation, tissue repair and remodeling. We used physiological and model cargos to quantify LDL uptake and assessed the effects of DecaBDE and HBCD on receptor mediated endocytosis, macropinocytosis, and phagocytosis. Pathway-specific pharmacological interventions and transcriptional profiling supported involvement of the above-mentioned signalling axis. Interestingly, based on prior work described in this thesis, TBBPA might have been expected to affect membrane-related functions such as endocytosis and pinocytosis, yet in our model TBBPA had no effect. TBBPA is a more amphipathic phenolic compound that remodels membrane organization at the interface but probably does not cross the threshold needed to depress macropinocytic flux. These contrasts argue against a simple rule that higher hydrophobicity yields greater toxicity and instead indicate that the chemical scaffold is a key determinant (98). Different FR classes can therefore elicit distinct effects, with some primarily reshaping membrane order and others directly limiting nutrient and lipoprotein entry through macropinocytosis.

Another core function of MQs is pathogen killing, which requires uptake of bacteria followed by intracellular lysis to eradicate infection (99). Uptake proceeds through phagocytosis with phagosome formation, maturation to the phagolysosome, acidification, and delivery of degradative enzymes; killing is supported by the oxidative burst and other ROS-dependent and -independent mechanisms (100, 101). Prior studies of FR exposure reported pro-oxidant nature of FRs via transcriptional responses, often framed through the Nrf2 signaling pathway (102-104). Our work challenges this by measuring biochemical events happening within one hour of exposure, implication direct enzymatic mechanisms. In particular, we showed that TCP reduced ROS production in human MQs, and that this reduction translated into impaired clearance of *Staphylococcus aureus*, while the phagocytic uptake step is unaffected. These findings add a functional dimension to immunotoxicity in this neglected field. This immunomodulatory effect is especially concerning for intracellular pathogens, where survival in MQs can produce a phenotype similar to chronic granulomatous disease (105). The clinical relevance of this effect motivates in vivo studies of intracellular bacterial infection, which we have planned for the future.

More FRs are being introduced to the market all the time and although some legacy compounds are now legally restricted, their environmental persistence means they continue to influence biological systems (106, 107). This highlights the need for meticulous immunotoxicological research with higher number of FRs. In my thesis, we examined sixteen FRs with different chemical structure for their impact on human MQs, and surprisingly few of them showed clear immunotoxic or immunomodulatory effects at the cellular level. On the other hand, these studies yielded as many as three novel, hitherto undescribed toxicity mechanisms for otherwise well-studied compounds, underscoring the importance of studying the complexity of the immune system in the context of environmental challenges. We can conclude that future

studies should also address how chemically similar POPs, such as TBBPA and BPA, can show very different effects (as in our case). With regard to model selection, MQs are a very diverse group of innate immune cells, residing in different tissues, with high plasticity and different functions (49). Therefore, we studied myeloid cell lines corresponding to various stages of differentiation along the monocyte-MQ axis, as well as unpolarized MQs, M1-polarized and M2-polarized ones. We also followed a comprehensive research scheme spanning molecular interactions, cellular and ultimately functional outcomes, using complementary methodology. A typical example is our approach to distinguishing bacterial uptake (phagocytosis) from clearance (killing), and using different cargos to assay three main membrane trafficking routes. In contrast, some previous studies reported diminished phagocytosis in THP-1 cell line without actual bacterial viability measurements (54). The limitations of our work involve the usual constraints of in vitro experiments, related to exposure mode, cell-cell interactions etc. The effects we discovered happen at concentrations that are non-cytotoxic and comparable to actual environmental burdens, but they are still relatively high and rarely achieved in biological systems and human bodies except in cases of accidental release or in occupational settings with elevated FR exposure. We also did not model in vivo pharmacokinetics. The exposure route (oral, dermal, or intravascular) was shown to produce different concentrations at the cellular site of action in animal models, and these route-specific differences were not captured in our in vitro experiments (108-110). Our work also focused on single compounds and did not evaluate mixtures. To mirror real world exposure, future studies should investigate defined mixtures of flame retardants to test for additive, synergistic, and antagonistic effects (111, 112). Still, our studies effectively filled a part of the knowledge gap in FR immunotoxicity and its main value lies in moving the field from purely observational or phenomenological studies to identification of molecular and cellular mechanisms, with emphasis on functional outcome. Together, these steps can improve translation, inform surveillance, guide safer chemical design, and help protect human immune health.

Conclusions

- The scope of immunotoxic properties among FRs and the severity of induced effects were lower in our study than might be anticipated from immune system complexity and expected threat level from recognized POPs.
- However, in the course of my thesis research we were able to identify three previously undescribed mechanisms of potential immunotoxicity by implementing investigations at molecular, cellular and functional level.
- The observed effects occurred at concentrations corresponding to environmental exposure levels in highly contaminated environments rather than typical daily conditions, indicating no immediate, broad urge for regulatory action while still emphasizing the need for focused risk analysis.
- We identified structure-dependent consequences of FR exposure in our research. More hydrophobic FRs primarily engaged membrane-associated processes, whereas more hydrophilic compounds preferentially acted within aqueous compartments.
- TBBPA affected plasma and intracellular membranes differently, underscoring the need to study compartmentally specific function and profile multiple membrane systems in biophysical toxicology assays.
- Some FRs may exert deleterious effects indirectly by selectively regulating the expression of signalling pathway elements. Impairment of macropinocytosis by DecaBDE occurs via specific transcriptional modulation rather than enzyme inhibition or global membrane cytotoxicity.
- Selective inhibition of LDL uptake via macropinocytosis in M2 MQs, without overall disruption of MQ metabolism or membrane integrity, has the potential to influence foam cell formation and atherosclerosis. The clinical significance of this pathway-specific effect should be further investigated.
- From the toxicological point of view, a narrow treatment of increase in ROS production as deleterious (and vice versa) is not justified in the case of immune cells, as illustrated by immunotoxicity of TCP mediated by inhibition of ROS production.
- Concurrent inhibition of reactive oxidant and ATP production, with no loss in phagocytotic capacity, leads to deficient pathogen killing in MQs and may turn them into safe havens for intracellular parasites or other pathogens.