ENVIRONMENTAL DEFENSE FUND, BREAST CANCER PREVENTION PARTNERS, CLEAN WATER ACTION, CONSUMER REPORTS, ENDOCRINE SOCIETY, ENVIRONMENTAL WORKING GROUP, HEALTHY BABIES BRIGHT FUTURES, MARICEL MAFFINI, AND LINDA BIRNBAUM

April 6, 2022

Dr. Dennis Keefe, Director
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
5100 Campus Drive
College Park, MD 20740-3835

Re: Refiling Food Additive Petition (FAP) No. 2B4831 asking FDA to remove or restrict its approvals of bisphenol A (BPA) (CASRN 80-05-7) pursuant to 21 USC § 348 with expedited review

Dear Dr. Keefe:

We are refiling[1] our January 27, 2022, Food Additive Petition (FAP) No. 2B4831[2] and supplementing it with information that addresses concerns raised by the Food and Drug Administration (FDA) in its February 22, 2022, letter[3] indicating it was not filing the petition. This supplement includes the following additional information:

- Recent epidemiology study showing that BPA exposure in utero is associated with increased risk of asthma and wheezing in school-age girls;
- Addition of hepatic uric acid as a tenth endpoint of concern where the benchmark dose is below FDA estimated exposure to BPA;
- Comments submitted to the European Food Safety Authority (EFSA);
- Additional studies provided to EFSA in comments; and
- Response to FDA's decision not to file our original filing.

We maintain that this petition fully complies with the requirements to 21 C.F.R. § 171.1. The new information reinforces our calls for an expedited review.

Recent epidemiology study showing that BPA exposure *in utero* is associated with increased risk of asthma and wheezing in school-age girls

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids' (Expert Panel) safety assessment established a new tolerable daily intake (TDI) of 0.04 ng of BPA per kilogram of body weight per day (ng/kg bw/d) and identified the immune system as the "most sensitive health outcome category to BPA exposure."[4] The TDI was based on a benchmark dose of 0.93 ng/kg bw/d for the response of Th17

[1] Our original filing and all related documents we provided FDA with that filing are incorporated by reference.
[2] FDA's Sylvia Proctor, Letter to Tom Neltner, February 1, 2022. The letter acknowledged receipt of petition on January 31, 2022, indicates the petition was dated January 27, 2022. The letter indicated the petition was designated FAP No. 2B4831. Petitioners will continue to use this number based on past practice with FDA.
[3] FDA's Marissa Lyn Santos, Letter to Tom Neltner, February 22, 2022.
[4] EFSA Panel on Food Contact Materials, Enzyme and Processing Aids (CEP) (Expert Panel), Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs, November 24, 2021 at https://connect.efsa.europa.eu/RM/s/publicconsultation2/a0l1v00000E8BRD/pc0109.

cells in female mice exposed in utero. For male mice, the benchmark dose was five times higher.[5] This gender difference is not surprising because BPA interferes with sex hormones and, therefore, their potential effects may be sex-dependent.[6]

The Expert Panel was particularly concerned about the Th17 cell response, stating that:

> T helper cells are key players in the immune-inflammatory chain of molecular events leading to amplification or suppression of specific immune elements, orienting the immune response towards effective resolution or chronic disease, and, according to an equilibrium in which these same cells and through the production of specific cytokines, restrict each other's own activity. . . Aberrant regulation of Th17 cells plays a significant role in the pathogenesis of multiple inflammatory and autoimmune disorders. The most notable role of IL-17 [interleukin 17] produced by Th17 cells is its involvement in inducing and mediating proinflammatory responses, associated with allergic responses. . . As such, numerous studies have shown that Th17 cells and their cytokines are also associated with the development of asthma. . . In addition, the activation of Th17 cells and the secretion of IL-17 can increase the immune response of Th2 cells, thereby aggravating the severity of allergic asthma.[7]

Despite these concerns, the Expert Panel did not develop a benchmark dose for allergic asthma because it judged the likelihood of BPA toxicity "as likely as not" (ALAN).[8] Only conclusions that were judged "likely" advanced to the benchmark dose calculation stage.

The ALAN designation for asthma/allergy was based on inconsistent findings in seven longitudinal human studies published between 2013 and 2018[9] assessing exposure during pregnancy. These studies had a cumulative sample size of 2,836 mother-child pairs, but the individual cohort ranged in number from 164 to 657 participants. Four of the seven showed statistically significant associations between asthma-related symptoms and BPA exposure and three did not.

On March 18, 2022, Abellan et al.[10] published a meta-analysis that combined eight European birth cohorts[11] with a total of 3,007 mother-child pairs where BPA concentrations in maternal urine samples were collected during pregnancy. With such a large cohort, the authors were able to analyze individual participant's data from all cohorts simultaneously thus strengthening the statistical power to evaluate potential associations between BPA exposure during pregnancy and asthma-related outcomes.

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[5] EFSA Expert Panel Report, Table 20.
[6] Lan, H.-C. et al. 2017. Bisphenol A disrupts steroidogenesis and induces a sex hormone imbalance through c-Jun phosphorylation in Leydig cells. Chemosphere. 185, 237–246. doi.org/10.1016/j.chemosphere.2017.07.004.
[7] EFSA Expert Panel Report, Section F.2.
[8] The Expert Panel found that the evidence showed allergic lung inflammation in animals was likely association with BPA exposure. See EFSA Expert Panel Report, Table 9.
[9] EFSA Expert Panel Report, Section 3.1.3.1. referencing Donohue et al., 2013 [RefID 10918]; Spanier et al., 2014b [RefID 6862]; Gascon et al., 2015 [RefID 2206]; Wang IJ et al., 2016 [RefID 7635]; Vernet et al., 2017 [RefID 7452]; Zhou AF et al., 2017 [RefID 9013]; Buckley et al., 2018 [RefID 11645]).
[10] Abellan A. et al. 2022. *In utero* exposure to bisphenols and asthma, wheeze, and lung function in school-age children: a prospective meta-analysis of 8 European birth cohorts. Environment International, 2022, 107178. doi.org/10.1016/j.envint.2022.107178. Including Supplementary Material.
[11] Generation R, The Netherlands (Jaddoe et al., 2006); INMA (INfancia y Medio Ambiente) Sabadell, INMA Gipuzkoa, INMA Valencia, Spain (Guxens et al., 2012); BiB (Born in Bradford), UK (Wright et al., 2013); EDEN (Etude des D´eterminants pr´e et post natals du d´eveloppement et de la sant´e de l'Enfant), France (Heude et al., 2016); MoBa (Norwegian Mother, Father and Child Cohort Study), Norway (Magnus et al., 2016; Paltiel et al., 2014); and RHEA (Mother- Child Cohort in Crete), Greece (Chatzi et al., 2017).

The authors found a statistically-significant association between *in utero* BPA exposure and both asthma and wheezing in school age girls with an odds ratio of 1.13 and 1.14 respectively. For school-aged boys, the odds ratio was slightly less than one. Specifically, Abellan et al. stated:

> Exposure to BPA was prevalent with 90% of maternal samples containing concentrations above detection limits. BPF and BPS [bisphenol F and bisphenol S] were found in 27% and 49% of samples. *In utero* exposure to BPA was associated with higher odds of current asthma (OR = 1.13, 95% CI = 1.01, 1.27) and wheeze (OR = 1.14, 95% CI = 1.01, 1.30) (p-interaction sex = 0.01) among girls, but not with wheezing patterns nor lung function neither in overall nor among boys. We observed inconsistent associations of BPF and BPS with the respiratory outcomes assessed in overall and sex-stratified analyses.
>
> *Conclusion:* This study suggests that *in utero* BPA exposure may be associated with higher odds of asthma and wheeze among school-age girls.[12]

This study reinforces the EFSA Expert Panel findings based on Luo et al., 2016[13] that the young female mouse pups with increased Th17 cells is not only relevant to human health but the endpoint selected was appropriate to establish the lowest benchmark dose.

Another similarity between the Luo et al. and Abellan et al., publications is that the BPA effects appear to persist. Luo et al. showed that the increase in Th17 cells observed at 21 days of age remained at 42 days in mice exposed in utero. Six of the eight cohorts included in the Abellan et al. meta-analysis had wheezing data on patients from one to four years of age and all had data on school age children (5-11 years).[14]

We note that the study by Abellan et al. was published a month after the comment period closed for the EFSA Expert Panel Report.

Addition of hepatic uric acid as a tenth endpoint of concern where the benchmark dose is below FDA estimated exposure to BPA

In our original filing, we identified the following nine endpoints of concern where the most protective benchmark dose (BMDL) established by the EFSA Expert Panel exceeded the estimated daily intake of 500 ng/kg bw/day that FDA developed in 2014 for populations two years or older. Sorted from greatest exceedance to least, the endpoints are as follows:

- Th17 cells endpoint in Luo et al. (2016)[15] for female mouse post-natal day 21 (PND21) with a BMDL of 0.93 ng/kg bw/day – 537 times lower than FDA's EDI;
- Th17 cells endpoint in Luo et al. (2016)[16] for female mouse post-natal day 42 (PND42) with a BMDL of 2.64 ng/kg bw/day – 189 times lower than FDA's EDI;
- Th17 cells endpoint in Luo et al. (2016)[17] for male mouse PND21 with a BMDL of 4.65 ng/kg bw/day – 108 times lower than FDA's EDI;

[12] Abellan et al., 2022.
[13] Luo Q. et al. 2017. Bisphenol A promotes hepatic lipid deposition involving Kupffer cells M1 polarization in male mice. Journal of Endocrinology 234(2), 143–154. doi:10.1530/JOE-17-0028.
[14] Abellan et al. 2022. Appendix A Supplementary data https://www.sciencedirect.com/science/article/pii/S0160412022001040?via%3Dihub#s0100
[15] Luo Q. et al. 2017. Bisphenol A promotes hepatic lipid deposition involving Kupffer cells M1 polarization in male mice. Journal of Endocrinology 234(2), 143–154. doi:10.1530/JOE-17-0028.
[16] Id.
[17] Id.

- Th17 cells endpoint in Luo et al. (2016)[18] for male mouse PND42 with a BMDL of 5.43 ng/kg bw/day – 92 times lower than FDA's EDI;
- Ratio of primordial and total ovarian follicles in Hu et al. (2018)[19] for mouse with a BMDL of 14.9 ng/kg bw/day – 33.5 times lower than FDA's EDI;
- Sperm motility endpoint in Wang HF et al. (2016)[20] for mouse with a BMDL of 53 ng/kg bw/day – 9.4 times lower than FDA's EDI;
- Ovary weight endpoint in Camacho et al. (2019)[21] for rat with BMDL of 104 ng/kg bw/day – 4.8 times lower than FDA's EDI;
- Sniffing incorrect holes on day 7 endpoint (learning and memory) in Johnson et al. (2016)[22] for male rats with BMDL of 243 ng/kg bw/day – 2.1 times lower than FDA's EDI; and
- Sperm viability endpoint in Wang HF et al. (2016)[23] for mouse with a BMDL of 405 – 1.2 times lower than FDA's EDI.

With this refiling, we are adding hepatic uric acid as a tenth endpoint of concern. It is related to metabolic effects. Based on Ma at al., 2018,[24] the BMDL is 24.6 ng/kg bw/day – 20 times lower than FDA's EDI.

Comments submitted to EFSA related to the ten endpoints of concern

EFSA sought public comments on the Expert Panel Report from December 15, 2021 to February 22, 2002. In March, the agency posted all the comments it received at https://open.efsa.europa.eu/consultation/a0c1v00000JA9rGAAT. The comments were organized by section of the Expert Panel Report with three comments listed per webpage for a total of 277 comments. Eighty-five of the comments included an attachment.

The numbers do not mean there were 277 distinct organizations submitting comments because an organization may have commented on multiple sections of the report and been listed many times. For example:

- Plastics Europe represented at least 34 comments and 17 attachments.
- American Chemistry Council represented at least 13 comments and 13 attachments.[25]
- German Federal Institute for Risk Assessment represented at least 12 comments and 12 attachments.

For FDA's reference, we copied the text for each of the comments and provide it with this filing as a spreadsheet titled "EFSA Comments Received Narrative – 3-1-22." We also combined the comments from the three organizations above in a single PDF to make it easier for FDA to review.

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[18] Id.
[19] Hu Y. et al. 2018. Bisphenol A initiates excessive premature activation of primordial follicles in mouse ovaries via the PTEN signaling pathway. Reproductive Sciences, 25(4), 609–620. doi:10.1177/1933719117734700.
[20] Wang HF. et al. 2016. Bisphenol A impairs mature sperm functions by a CatSper-relevant mechanism. Toxicological Sciences, 152(1), 145–154. doi:10.1093/toxsci/kfw070.
[21] Camacho L. et al. 2019. A two-year toxicology study of bisphenol A (BPA) in Sprague-Dawley rats: CLARITY-BPA core study results. Food and Chemical Toxicology, 132. 110728. https://doi.org/10.1016/j.fct.2019.110728
[22] Johnson SA. et al. 2016. Effects of developmental exposure to bisphenol A on spatial navigational learning and memory in rats: A CLARITY-BPA study. Hormones and Behavior, 80, 139–148. doi:10.1016/j.yhbeh.2015.09.005.
[23] Wang HF. et al. 2016.
[24] Ma L. et al. 2018. Bisphenol A promotes hyperuricemia via activating xanthine 13839 oxidase. FASEB Journal 32(2), 1007–1016. doi:10.1096/fj.201700755R. Copy of study provided in original filing.
[25] The same reference was provided attached to 13 comments.

Please note that EFSA's comment system designated a comment author as "Respondent Requested Anonymity" by default unless the organization specifically requested to be named publicly. Where the organization's comment or attachment specifically named the organization – as is the case for Plastics Europe – we assigned that name to the spreadsheet. There were 190 comments where the default anonymous designation was left in place.

Additional studies provided to EFSA in comments

Several comments submitted to EFSA identified additional studies that were published after October 15, 2018, when the agency closed the opportunity to submit information in its initial call for studies. We describe below all the additional studies submitted by the commenters related to any of our ten endpoints of concern described above that we were able to find.

1. ***Dong, Y-D. et al. 2020. Abnormal differentiation of regulatory T cells and Th17 cells induced by perinatal bisphenol A exposure in female offspring mice. Molecular and Cellular Toxicology 16:167-174. https://doi.org/10.1007/s13273-019-00067-4.***

   Background
   Bisphenol A (BPA) is an environmental estrogen widely exposed to human beings, and there are more studies on its reproductive toxicity, endocrine disruption and neurobehavioral disorders. Recent few studies have found that BPA has immunotoxicity, and its mechanism is not clear. Therefore, the effects of BPA on immune system have attracted extensive attention. The aim of this study was to investigate the effect and mechanism of perinatal exposure to BPA on regulatory T cells (Treg) and Th17 cells in female offspring mice.

   Methods
   Twenty-one pregnant C57BL/6 mice were randomly divided into three groups: a control group, low-dose BPA (0.2 μg/mL) and high-dose BPA (2.0 μg/mL) exposure group. All received BPA exposure via drinking water from gestational day 6 to the end of lactation. Female offspring were fed a normal diet and drinking water for 1 month. The percentages of Treg and Th17 cells, the levels of Foxp3 and RORγt protein and IL-17 and TGF-β from spleen tissue or blood were measured in female offspring.

   Results
   The percentage of Treg cells and levels of Foxp3 protein decreased, while the percentage of Th17 cells and levels of RORγt protein increased, which showed a dose–effect relationship. The levels of serum TGF-β were significantly lower and the levels of serum IL-17 were statistically higher in BPA-exposed female offspring compared with controls ($P < 0.05$ or $P < 0.01$). But there were no statistical difference in the levels of serum TGF-β and IL-17 between 0.2 μg/mL and 2.0 μg/mL BPA groups ($P > 0.05$).

   Conclusion
   BPA exposure during pregnancy and lactation could cause abnormal differentiation and function of Treg and Th17 cells in female offspring mice, which was associated with down-regulated Foxp3 and up-regulated RORγt protein, respectively. Our findings indicated that BPA exposure during early development may play an important role in the development of autoimmune diseases later.

   Petitioner's Assessment: Reinforces evidence that BPA impacts Th17 and provides additional insight into mechanisms that BPA may cause harm. Supports Expert Panel's conclusions that BPA is toxic to the immune system.

2. ***Gao, L. et al. 2020. The imbalance of Treg/Th17 cells induced by perinatal bisphenol A exposure is associated with activation of the PI3K/Akt/mTOR signaling pathway in male offspring mice. Food and Chemical Toxicology 137:111177. https://doi.org/10.1016/j.fct.2020.111177.***

   Bisphenol A (BPA) can inhibit the differentiation and function of regulatory T cells (Treg), and affect the balance of helper T cell (Th) 1/Th2, therefore, the immunotoxicity of BPA has attracted widespread attention in recent years, but its mechanism is not clear. The main aim of this study was to explore the regulatory mechanism of the PI3K/Akt/mTOR signaling pathway in the context of perinatal exposure to BPA-induced Treg/Th17 imbalance in male offspring mice through a combination of *in vivo* and *in vitro* methods. Our results showed that perinatal exposure to BPA could increase the number of Th17 cells while decreasing Treg cell numbers, which was consistent with the expression levels of up-regulation of RORγt protein and a down-regulation FOXP3 protein in the splenocytes of the male offspring mice. BPA could activate the PI3K/Akt/mTOR signaling pathway and increase the inflammatory response, as evidenced by higher serum IL-17 and TNF-α levels by inducing the activation of the AhR and TLR4/NF-κB signaling pathways. Moreover, our results also supported the hypothesis whereby the Treg/Th17 imbalance, induced by perinatal exposure to BPA, was associated with the activation of PI3K/Akt/mTOR signaling *in vitro*-cultured peripheral blood mononuclear cells by using rapamycin as an inhibitor of mTOR.

   Petitioner's Assessment: Reinforces evidence that BPA increases Th17 and provides additional insight into the molecular mechanisms by which BPA may cause harm. Supports Expert Panel's conclusions that BPA is toxic to the immune system.

3. ***Malaise, Y. et al. 2020. Oral exposure to bisphenols induced food intolerance and colitis in vivo by modulating immune response in adult mice. Food and Chemical Toxicology 146:111773. https://doi.org/10.1016/j.fct.2020.111773.***

   Bisphenol (BP) A, a known food contaminant, is a possible risk factor in the epidemic of non-communicable diseases (NCD) including food intolerance and inflammatory bowel diseases (IBD). Regulatory restrictions regarding BPA usage led to BPA removal and replacement by poorly described substitutes, like BPS or BPF (few data on occurrence in food and human samples and biological effect). Oral tolerance protocol to ovalbumin (OVA) in WT mice and *Il10*$^{-/-}$ mice prone to IBD were used respectively to address immune responses towards food and microbial luminal antigens following BP oral exposure. Both mice models were orally exposed for five weeks to BPA, BPS or BPF at 0.5, 5 and 50 µg/kg of body weight (bw)/day (d). Oral exposure to BPs at low doses (0.5 and 5 µg/kg bw/d) impaired oral tolerance as indicated by higher humoral and pro-inflammatory cellular responses in OVA-tolerized mice. However, only BPF exacerbate colitis in *Il10*$^{-/-}$ prone mice associated with a defect of fecal IgA and increased secretion of TNF-α in colon. These findings provide a unique comparative study on effects of adult oral exposure to BPs on immune responses and its consequences on NCD related to intestinal luminal antigen development.

   Petitioner's Assessment: Provides additional insight into BPA's mechanism of action that results in harm. Supports Expert Panel's conclusions that BPA is toxic to the immune system. Indicates that two chemical substitutes, BPS and BPF, have similar effects on immune system.

4. ***Malaise, Y. et al. 2020. Perinatal oral exposure to low doses of bisphenol A, S or F impairs immune functions at intestinal and systemic levels in female offspring mice. Environmental Health 19:93. https://doi.org/10.1186/s12940-020-00614-w.***

Background
Bisphenol A (BPA), one of the highest-volume chemicals produced worldwide, has been identified as an endocrine disruptor. Many peer-reviewing studies have reported adverse effects of low dose BPA exposure, particularly during perinatal period (gestation and/or lactation). We previously demonstrated that perinatal oral exposure to BPA (via gavage of mothers during gestation and lactation) has long-term consequences on immune response and intestinal barrier functions. Due to its adverse effects on several developmental and physiological processes, BPA was removed from consumer products and replaced by chemical substitutes such as BPS or BPF, that are structurally similar and not well studied compare to BPA. Here, we aimed to compare perinatal oral exposure to these bisphenols (BPs) at two doses (5 and 50 µg/kg of body weight (BW)/day (d)) on immune response at intestinal and systemic levels in female offspring mice at adulthood (Post Natal Day PND70).

Methods
Pregnant female mice were orally exposed to BPA, BPS or BPF at 5 or 50 µg/kg BW/d from 15th day of gravidity to weaning of pups at Post-Natal Day (PND) 21. Humoral and cellular immune responses of adult offspring (PND70) were analysed at intestinal and systemic levels.

Results
In female offspring, perinatal oral BP exposure led to adverse effects on intestinal and systemic immune response that were dependant of the BP nature (A, S or F) and dose of exposure. Stronger impacts were observed with BPS at the dose of 5 µg/kg BW/d on inflammatory markers in feces associated with an increase of anti-E. coli IgG in plasma. BPA and BPF exposure induced prominent changes at low dose in offspring mice, in term of intestinal and systemic immune responses, provoking an intestinal and systemic Th1/Th17 inflammation.

Conclusion
These findings provide, for the first time, results of long-time consequences of BPA, S and F perinatal exposure by oral route on immune response in offspring mice. This work warns that it is mandatory to consider immune markers and dose exposure in risk assessment associated to new BPA's alternatives.

Petitioner's Assessment: Supports Expert Panel's conclusions that BPA is toxic to the immune system. Indicates that two chemical substitutes, bisphenol S and bisphenol F, have similar effects on the immune system.

5. ***Malaise, Y. et al. 2020. Differential influences of the BPA, BPS and BPF on in vitro IL-17 secretion by mouse and human T cells. Toxicology in Vitro 69:104193. https://doi.org/10.1016/j.tiv.2020.104993.***

The endocrine disruptor and food contaminant bisphenol A (BPA) is frequently present in consumer plastics and can produce several adverse health effects participating in the development of inflammatory and autoimmune diseases. Regulatory restrictions have been established to prevent risks for human health, leading to the substitution of BPA by structural analogues, such as bisphenol S (BPS) and F (BPF). In this study, we aimed at comparing the *in vitro* impact of these bisphenols from 0.05 to 50,000 nM on Th17 differentiation, frequency and function in mouse systemic and intestinal immune T cells and in human blood T cells. This study reports the

ability of these bisphenols, at low and environmentally relevant concentration, *i.e*, 0.05 nM, to increase significantly IL-17 production in mouse T cells but not in human T lymphocytes. The use of an aryl hydrocarbon receptor (AhR) specific inhibitor demonstrated its involvement in this bisphenol-induced IL-17 production. We also observed an increased IL-17 secretion by BPS and BPF, and not by BPA, in mouse naive T cells undergoing *in vitro* Th17 differentiation. In total, this study emphasizes the link between bisphenol exposures and the susceptibility to develop immune diseases, questioning thus the rational of their use to replace BPA.

Petitioner's Assessment: Reinforces evidence that BPA increases Th17 and provides additional insight into mechanisms that BPA may cause harm. Indicates that two chemical substitutes, BPS and BPF, have similar effects on immune system. Supports Expert Panel's conclusions that BPA is toxic to the immune system.

6. ***Malaise, Y. et al. 2021. Bisphenol A, S or F mother's dermal impregnation impairs offspring immune responses in a dose and sex-specific manner in mice. Scientific Reports 11:1650. https://doi.org/10.1038/s41598-021-81231-6.***

Bisphenol (BP)A is an endocrine disruptor (ED) widely used in thermal papers. Regulatory restrictions have been established to prevent risks for human health, leading to BPA substitution by structural analogues, like BPS and BPF. We previously demonstrated that oral perinatal exposure to BPA had long-term consequences on immune responses later in life. It appears now essential to enhance our understanding on immune impact of different routes of BP exposure. In this study, we aimed at comparing the impact of mother dermal exposure to BPs on offspring immune system at adulthood. Gravid mice were dermally exposed to BPA, BPS or BPF at 5 or 50 µg/kg of body weight (BW)/day (d) from gestation day 15 to weaning of pups at post-natal day (PND)21. In offspring, BPs dermal impregnation of mothers led to adverse effects on immune response at intestinal and systemic levels that was dependent on the BP, the dose and offspring sex. These findings provide, for the first time, results on long-term consequences of dermal perinatal BPs exposure on immune responses in offspring. This work warns that it is mandatory to consider immune markers, dose exposure as well as sex in risk assessment associated with new BPA's alternatives.

Petitioner's Assessment: Demonstrates that dermal exposure to BPA is also a route of exposure and indicates that two chemical substitutes, BPS and BPF, have similar effects on immune system. Supports Expert Panel's conclusions that BPA is toxic to the immune system.

7. ***Wang, G. et al. 2020. Maternal vitamin D supplementation inhibits bisphenol A-induced proliferation of Th17 cells in adult offspring. Food and Chemical Toxicology 144:111604. https://doi.org/10.1016/j.fct.2020.111604.***

Bisphenol A (BPA) exposure can increase the risk of immune-related diseases in later life. Vitamin D3 (Vit D3) has been shown to have multiple immunomodulatory actions and has been used to treat immune diseases. However, the potential beneficial effects of Vit D3 on BPA-induced adverse effects in the immune system have not explored. We hypothesize that VitD3 may ameliorate BPA-induced side effects in the immune system, even in offspring of VitD3-supplemented mothers. Here, we established our experimental model by exposing pregnant dams with 1000 nM BPA with or without VitD3 (0.25 µg/kg, 1 µg/kg and 4 µg/kg) treatment. We show that mother's exposure to BPA increases proliferation of the spleen T helper 17 (Th17) cells and serum protein level of IL-17 in the offspring; however, VitD3 supplementation in mothers dose-dependently ameliorated these BPA-induced side effects on the immune system in the offspring

as evidenced by attenuated upregulation of Th17 proliferation, and *RORγt*, IL-17, IL-6, and IL-23 expressions in the offspring. Our data provide the first evidence that maternal VitD3 supplementation offers benefits to the offspring by attenuating BPA-induced side effects on the immune system through vitamin D receptor (VDR)-dependent regulation of transcription factors and cytokines, suggesting its translational potential.

Petitioner's Assessment: Supports Expert Panel's conclusions that BPA is toxic to the immune system. Indicates that Vitamin D supplementation in diet may reduce immune system harm posed by BPA.

8. ***Wang, G. 2022. The role of metabolism in Th17 cell differentiation and autoimmune diseases. International Immunopharmacology 103:108450. https://doi.org/10.1016/j.intimp.2021.108450.***

T helper 17 cells (Th17) have been associated with the pathogenesis of autoimmune and inflammatory diseases, which makes them become a sharp focus when the researchers are seeking therapeutic target for these diseases. A growing body of evidence has suggested that cellular metabolism dictates Th17 cell differentiation and effector function. Moreover, various studies have disclosed that metabolism is linked to the occurrence of autoimmune diseases. In this article, we reviewed the most recent findings regarding the importance of metabolism in Th17 cell differentiation and autoimmune diseases and also discussed the modulation mechanisms of glycolysis, fatty acid and cholesterol synthesis, and amino acids metabolism for Th17 cell differentiation. This review summarized the potential therapeutic or preventing strategies for Th17 cell-mediated autoimmune diseases.

Petitioner's Assessment: Supports Expert Panel's conclusions that Th17 cell endpoint is relevant to immunotoxicity.

9. ***Yanagisawa, R. et al. 2019. Oral exposure to low dose bisphenol A aggravates allergic airway inflammation in mice. Toxicology Reports 6:1253-1262. https://doi.org/10.1016/j.toxrep.2019.11.012.***

Bisphenol A (BPA) is widely used in many consumer products and has adverse effects on human health including allergic diseases. We investigated the effects of low dose BPA, comparable to actual human oral exposure, on allergic asthma in mice. C3H/HeJ male mice were fed a chow diet containing BPA (equivalent to 0.09, 0.90, or 9.01 μg/kg/day) and were intratracheally administered ovalbumin (OVA, 1 μg/animal) every two weeks from 5–11 weeks of age. All doses of BPA plus OVA enhanced pulmonary inflammation and airway hyperresponsiveness, and increased lung mRNA levels of Th2 cytokine/chemokine, and serum OVA-specific IgE and IgG_1 compared to OVA alone, with greater effects observed in the middle- and high-dose BPA plus OVA groups. Furthermore, high-dose BPA with OVA decreased lung mRNA levels of ERβ and AR compared with OVA. Furthermore, BPA enhanced OVA-restimulated cell proliferation and protein levels of IL-4 and IL-5 in mediastinal lymph node (MLN) cells in OVA-sensitized mice. In bone marrow (BM) cells, middle-dose BPA with OVA increased Gr-1 expression. In conclusion, oral exposure to low-dose BPA at levels equivalent to human exposure can aggravate allergic asthmatic responses through enhancement of Th2-skewed responses, lung hormone receptor downregulation, and MLN and BM microenvironment change.

Petitioner's Assessment: Reinforces evidence of harm from BPA and association with allergic asthma. Supports Expert Panel's conclusions that BPA is toxic to the immune system.

10. ***Zhang, S. et al. 2021. The Alterations in and the Role of the Th17/Treg Balance in Metabolic Diseases. Frontiers in Immunology 12:678355. https://doi.org/10.3389/fimmu.2021.678355***

Chronic inflammation plays an important role in the development of metabolic diseases. These include obesity, type 2 diabetes mellitus, and metabolic dysfunction-associated fatty liver disease. The proinflammatory environment maintained by the innate immunity, including macrophages and related cytokines, can be influenced by adaptive immunity. The function of T helper 17 (Th17) and regulatory T (Treg) cells in this process has attracted attention. The Th17/Treg balance is regulated by inflammatory cytokines and various metabolic factors, including those associated with cellular energy metabolism. The possible underlying mechanisms include metabolism-related signaling pathways and epigenetic regulation. Several studies conducted on human and animal models have shown marked differences in and the important roles of Th17/Treg in chronic inflammation associated with obesity and metabolic diseases. Moreover, Th17/Treg seems to be a bridge linking the gut microbiota to host metabolic disorders. In this review, we have provided an overview of the alterations in and the functions of the Th17/Treg balance in metabolic diseases and its role in regulating immune response-related glucose and lipid metabolism.

Petitioner's Assessment: Reinforces significance of Th17 on immune system. Supports Expert Panel's conclusions that BPA is toxic to the immune system.

11. ***Aparicio-Soto, M. et al. 2020. TCRs with segment TRAV9-2 or a CDR3 histidine are overrepresented among nickel-specific CD4+ T cells. Allergy 75:2574-2586. https://doi.org/10.1111/all.14322.***

Background
Nickel is the most frequent cause of T cell–mediated allergic contact dermatitis worldwide. *In vitro*, CD4+ T cells from all donors respond to nickel but the involved αβ T cell receptor (TCR) repertoire has not been comprehensively analyzed.

Methods
We introduce CD154 (CD40L) upregulation as a fast, unbiased, and quantitative method to detect nickel-specific CD4+ T cells ex vivo in blood of clinically characterized allergic and non allergic donors. Naïve (CCR7+ CD45RA+) and memory (not naïve) CD154+ CD4+ T cells were analyzed by flow cytometry after 5 hours of stimulation with 200 μmol/L $NiSO_4$., TCR α- and β-chains of sorted nickel-specific and control cells were studied by high-throughput sequencing.

Results
Stimulation of PBMCs with $NiSO_4$ induced CD154 expression on ~0.1% (mean) of naïve and memory CD4+ T cells. In allergic donors with recent positive patch test, memory frequencies further increased ~13-fold and were associated with markers of in vivo activation. CD154 expression was TCR-mediated since single clones could be specifically restimulated. Among nickel-specific CD4+ T cells of allergic and non allergic donors, TCRs expressing the α-chain segment TRAV9-2 or a histidine in their α- or β-chain complementarity determining region 3 (CDR3) were highly overrepresented.

Conclusions
Induced CD154 expression represents a reliable method to study nickel-specific CD4+ T cells. TCRs with particular features respond in all donors, while strongly increased blood frequencies indicate nickel allergy for some donors. Our approach may be extended to other contact allergens for the further development of diagnostic and predictive in vitro tests.

Petitioner's Assessment: Reinforces significance of Th cells on allergic reactions.

12. ***Marcinkowska, E. 2020. The Vitamin D System in Humans and Mice: Similar but Not the Same. Reports 3:1. https://doi.org/10.3390/reports3010001.***

    Vitamin D is synthesized in the skin from 7-dehydrocholesterol subsequently to exposure to UVB radiation or is absorbed from the diet. Vitamin D undergoes enzymatic conversion to its active form, 1,25-dihydroxyvitamin D (1,25D), a ligand to the nuclear vitamin D receptor (VDR), which activates target gene expression. The best-known role of 1,25D is to maintain healthy bones by increasing the intestinal absorption and renal reuptake of calcium. Besides bone maintenance, 1,25D has many other functions, such as the inhibition of cell proliferation, induction of cell differentiation, augmentation of innate immune functions, and reduction of inflammation. Significant amounts of data regarding the role of vitamin D, its metabolism and VDR have been provided by research performed using mice. Despite the fact that humans and mice share many similarities in their genomes, anatomy and physiology, there are also differences between these species. In particular, there are differences in composition and regulation of the VDR gene and its expression, which is discussed in this article.

    Petitioner's Assessment: Supports Expert Panel's conclusions that BPA is toxic to the immune system. Indicates that Vitamin D supplementation in diet may help reduce immune system harm posed by BPA.

13. ***Moreno-Cordova, V. et al. 2021. Th17 Lymphocytes in Children with Asthma: Do They Influence Control? Pediatric Allergy, Immunology, and Pulmonology 34, 4. https://doi.org/10.1089/ped.2021.0067.***

    Background: Allergic asthma was considered as an inflammation mediated by specific CD4+ helper lymphocytes (Th2); however, this paradigm changed in 2005, when a third group of helper cells called Th17 cells were identified. Th17 lymphocytes are the main source of interleukin (IL)-17A–F, IL-21, and IL-22; however, their physiological role in children is unclear. This study aimed to determine the percentage of Th17 cells and IL-17A in pediatric patients diagnosed with asthma and to associate it with disease control using a validated questionnaire.

    Methods: This cross-sectional, prospective, comparative study included 92 asthma-diagnosed children 4–18 years of age. The Asthma Control Test was used as an assessment measure to classify patients as controlled (n = 30), partially controlled (n = 31), and uncontrolled (n = 31). Th17 cells and IL-17A were analyzed by flow cytometry. Patients receiving inhaled steroid therapy as monotherapy or associated with a long-acting bronchodilator were included.

    Results: The mean percentage of Th17 cells in the participants was 4.55 – 7.34 (Controlled), 5.50 – 8.09 (Partially Controlled), and 6.14 – 7.11 (Uncontrolled). There was no significant difference between the 3 groups (P = 0.71). The mean percentage of IL-17A in all the participants was 9.84 – 9.4 (Controlled), 10.10 – 10.5 (Partially Controlled), and 11.42 – 8.96 (Uncontrolled); no significant difference between the 3 groups (P = 0.79) was observed. Th17 lymphocyte levels were similar among the 3 groups and the same trend was observed with IL-17A. A significant correlation between Th17 or IL-17A and the degree of asthma control (Th17, P = 0.24; IL-17A, P = 0.23) was not found.

Conclusions: The percentages of both Th17 lymphocytes and IL-17A found in children with asthma were not significantly different in the 3 groups, which suggests that they do not play an important role in asthma control. Our findings may contribute to the knowledge related to non-Th2 inflammation in children. Clinical-Trials.gov ID: 2015-2102-85.

Petitioner's Assessment: Contributes to the evidence on the role of Th17 cells in asthma in children. The effect is not significantly different between the groups likely due to the small size cohort. Nonetheless, the percentage of Th17 cells and IL-17A increase in children with less controlled asthma.

14. ***Wildner, G. 2019. Are rats more human than mice? Immunobiology 224:172-176. https://doi.org/10.1016/j.imbio.2018.09.002.***

In contrast to rats, mouse models are nowadays generally used for the investigation of immune responses and immune-mediated diseases, there are many different strains and mouse-specific tools available, and it is easy to generate transgenic and constitutive or inducible knockout mice for any gene. Many immune markers and mechanisms have been detected in mice and have been introduced as gold standard in immunology, however, some turned out to be not unconditionally transferable to the human immune system.

Rats have been used more frequently in former days but are mostly outstripped by mice due to the fact that fewer strains are available, they need more space than mice, are more expensive to maintain and breed, and it is extremely difficult to generate transgenic or ko-rats. Consequently, the choice of rat-specific diagnostic tools like antibodies is quite poor and most researchers have switched to mouse models for the investigation of immune mechanisms, while rats are still widely used for toxicology by the pharmaceutical industry. However, it should be taken into consideration that there are some immunological similarities between rats and humans that are not presented in mice. Some of them like MHC class II and Foxp3 expression by activated effector T cells we have detected during our research on the immune response of rat models of experimental autoimmune uveitis.

Petitioner's Assessment: Commentary comparing similarities and differences on narrow aspects of the immune system between human and two rodent species.

15. ***Major, T.J. et al. 2018. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. BMJ 363:k3951. http://dx.doi.org/10.1136/bmj.k3951.***

Objective
To systematically test dietary components for association with serum urate levels and to evaluate the relative contributions of estimates of diet pattern and inherited genetic variants to population variance in serum urate levels.

Design
Meta-analysis of cross sectional data from the United States.

Data sources
Five cohort studies.

Review methods
16,760 individuals of European ancestry (8414 men and 8346 women) from the US were included in analyses. Eligible individuals were aged over 18, without kidney disease or gout, and

not taking urate lowering or diuretic drugs. All participants had serum urate measurements, dietary survey data, information on potential confounders (sex, age, body mass index, average daily calorie intake, years of education, exercise levels, smoking status, and menopausal status), and genome wide genotypes. The main outcome measures were average serum urate levels and variance in serum urate levels. β values (95% confidence intervals) and Bonferroni corrected P values from multivariable linear regression analyses, along with regression partial R2 values, were used to quantitate associations.

Results
Seven foods were associated with raised serum urate levels (beer, liquor, wine, potato, poultry, soft drinks, and meat (beef, pork, or lamb)) and eight foods were associated with reduced serum urate levels (eggs, peanuts, cold cereal, skim milk, cheese, brown bread, margarine, and non-citrus fruits) in the male, female, or full cohorts. Three diet scores, constructed on the basis of healthy diet guidelines, were inversely associated with serum urate levels and a fourth, data driven diet pattern positively associated with raised serum urate levels, but each explained ≤0.3% of variance in serum urate. In comparison, 23.9% of variance in serum urate levels was explained by common, genome wide single nucleotide variation.

Conclusion
In contrast with genetic contributions, diet explains very little variation in serum urate levels in the general population.

Petitioner's Assessment: Added for completeness

We note that comments from the German Federal Institute for Risk Assessment included the following reference: "Wei et al., 2021" in the context of Th17 cells and benchmark dose analysis discussion. We were unable to identify the full reference. Below is a screen shot of the comment submitted to EFSA.

Annex I	Benchmark dose analysis	Line 209, p. 8	The figures from Sorrenti et al. (2016) are not correct. The values for Th-reg and Th17 in Table IIIA are switched. The cited Th17 cell reference frequency with a mean of 10.5 % seems rather high compared to other studies (Milovanovic et al., 2010: ~2%; Wei et al., 2021: ~0,25% (children)).	

FDA's decision not to file our original submission was incorrect.

On February 22, 2022, FDA notified the petitioners that it was "not filing this petition because of incomplete information."[26] The agency explained its decision by stating:

> Under Section 409(b)(2)(E) of the Federal Food, Drug, and Cosmetic Act, a food additive petition is required to include "full reports of investigations made with respect to the safety for use of such additive." Our regulations, at 21 CFR 171.1(c)E, state that a "petition may be regarded as incomplete unless it includes full reports of adequate tests reasonably applicable to show whether or not the food additive will be safe for its intended use," and further provide that it "shall not omit without explanation any reports of investigations that would bias an evaluation of the safety of the food additive."
>
> Your food additive petition does not include full reports of adequate tests reasonably applicable to address the safety of BPA for its intended use. The petition is based on a draft opinion, which is

[26] FDA's Marissa Lyn Santos, Letter to Tom Neltner, February 22, 2022.

> open for public comment, by the European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes and Processing Aids. It would be premature for FDA to consider this draft opinion in reviewing a food additive petition. As such, the data and information in the petition is incomplete and insufficient for performing a comprehensive evaluation.[27]

We disagree with FDA's decision. We provided the agency with full reports of investigations into the safety of BPA.

FDA's decision is confusing because the agency is obligated under the law to make its own independent judgment based on the evidence and its regulation. We have not asked before, and neither do we ask now, that FDA adopt the evaluation and conclusions made by another government body without evaluation of our petition. Rather, our petition is based on our evaluation of the evidence included in the EFSA draft risk evaluation. In our petition, we affirm the conclusions that were developed and unanimously supported by the 17 scientists who serve on EFSA's Expert Panel.

FDA's regulations at 21 C.F.R. 170.3(i) state that:

> *Safe* or *safety* means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use.
> It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:
> (1) The probable consumption of the substance and of any substance formed in or on food because of its use.
> (2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
> (3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

In the case of the Expert Panel Report, 17 scientists selected by EFSA reached a unanimous decision and were sufficiently confident in the analysis that they had EFSA make it available for public comment. EFSA selected these scientists, only after declaring their interests and being screened for conflicts of interest, based on their expertise in the following areas:

- "Chemical risk assessment focusing on food enzymes, and chemicals used in the production of plastic materials or other food packaging
- Toxicology (mammalian): sub-chronic and chronic toxicity (repeated dose studies), genotoxicity and mutagenicity, developmental and reproductive toxicity, carcinogenicity, allergenicity and immunotoxicity
- Toxicity testing in experimental animals and alternative toxicity tests
- Toxicokinetics and toxicodynamics (ADME - absorption, distribution, metabolism, excretion) of substances
- Epidemiology (humans)
- Chemistry (organic, analytical and synthetic chemistry), especially for the chemical identification and specification of chemical substances and for migration testing of food contact materials
- Exposure assessment and consumption surveys
- Food technology (manufacturing processes and use of processing aids)

[27] FDA's Marissa Lyn Santos, Letter to Tom Neltner, February 22, 2022.

- Food microbiology including enzyme biotechnology using genetically-modified microorganisms"[28]

Based on their analysis, these 17 eminently competent scientists not only found that there was no longer a reasonable certainty in their minds that the levels of BPA found in the diet were safe under the conditions of its intended use, but also "**concluded that there is a health concern from dietary BPA exposure for all age groups**." [Emphasis added]

For FDA to dismiss this analysis and our petition as somehow incomplete is not credible. FDA should not and must not wait to see what the final EFSA risk evaluation would be. The fact that EFSA's Expert Panel Report on its reevaluation of the risks to public health related to the presence of BPA in food was a draft and open for public comment does not make it less than a full report. The Expert Panel may modify its analysis when it finalizes the risk evaluation at some time in the future, but that does not undermine the reality or the credibility that it is a full report of its investigations available at the time.

The evidence presented in our petition should be sufficient to compel FDA to act without delay.

Additional evidence generated since original submission strengthens need for action.

Without regard to FDA's flawed reasoning, because EFSA has posted the public comments it received, we now include those to fulfill our obligations to provide full reports of investigations made with respect to the safety of BPA. We also note that almost all of the scientific studies provided by the commenters were related to immunotoxicity, support EFSA's selection of Th17 cells as the most sensitive endpoint and corresponding 100,000 fold reduction of its TDI, and reinforce the need for immediate action.

In addition, we include a new epidemiology study[29] that makes our demand for expedited review even more compelling. It found that school-age girls exposed to BPA during gestation have statistically significant higher odds of asthma and wheezing – a finding that reflects the similarities with the studies EFSA's Expert Panel relied on to establish the TDI of 0.04 ng/kg bw/d – a level that is 12,500 times lower than FDA's estimated daily intake of BPA for people two or more years of age of 500 ng/kg bw/d.

The bottom line is that evidence we present in the petition indicates that the use of BPA in contact with food is unsafe and the data that has emerged through the public comments on EFSA's Expert Panel report and human study make clear that FDA must move forward and fulfill its responsibilities to protect the public health by ensuring the safety of our nation's food supply. If FDA believes inconsistencies remain in the totality of the evidence, that is further indication that the reasonable certainty of no harm safety standard for BPA is no longer met.

For your convenience, Attachment A contains the list of references described in this document, new references submitted to EFSA by commenters, and comments submitted to EFSA compiled by the petitioners.

If you have questions or comments, please contact Tom Neltner at tneltner@edf.org and Dr. Maricel Maffini at drmvma@gmail.com on all responses.

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[28] EFSA, Food Contact Materials, Enzyme and Processing Aids, accessed on March 26, 2022 at https://www.efsa.europa.eu/en/science/scientific-committee-and-panels/cep#:~:text=The%20Panel%20on%20Food%20Contact%20Materials%2C%20Enzymes%20and,their%20use%20can%20be%20authorised%20in%20the%20EU.

[29] Abellan et al., 2022.

Sincerely,

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Attachment A
List of References

A) References mentioned in the original petition and already considered by the EFSA Expert Panel

1. Lan, H-C. et al. 2017. Bisphenol A disrupts steroidogenesis and induces a sex hormone imbalance through c-Jun phosphorylation in Leydig cells. Chemosphere 185:237-246. doi.org/10.1016/j.chemosphere.2017.07.004.
2. Donohue, KM. et al. 2013. Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. J Allergy Clin Immunol. 2013 Mar;131(3):736-42. 10.1016/j.jaci.2012.12.1573.
3. Spanier, AJ. et al. Bisphenol A exposure and the development of wheeze and lung function in children through age five years. JAMA Pediatr. 168:1131-37. doi:10.1001/jamapediatrics.2014.1397.
4. Gascon, M. et al. 2015. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol 135:370-378 http://dx.doi.org/10.1016/j.jaci.2014.09.030.
5. Wang, I.J. et al. 2016. Bisphenol A exposure may increase the risk of development of atopic disorders in children. Int J Hyg Environ Health 219:311-316. doi:10.1016/j.ijheh.2015.12.001.
6. Vernet, C. et al. 2017. In Utero Exposure to Select Phenols and Phthalates and Respiratory Health in Five-Year-Old Boys: A Prospective Study. Environ Health Perspect. 125:097006. doi:10.1289/EHP1015.
7. Zhou, AF. et al. 2017. Prenatal exposure to bisphenol A and risk of allergic diseases in early life. Pediatric Research 81:851-856. doi:10.1038/pr.2017.20.
8. Buckley, JP. et al. 2018. Associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic diseases among children aged 6 and 7 years. Environment International 115:79-88. https://doi.org/10.1016/j.envint.2018.03.016.
9. Luo, Q. et al. 2017. Bisphenol A promotes hepatic lipid deposition involving Kupffer cells M1 polarization in male mice. Journal of Endocrinology 234:143-154. doi:10.1530/JOE-17-0028.
10. Hu, Y. et al. 2018. Bisphenol A initiates excessive premature activation of primordial follicles in mouse ovaries via the PTEN signaling pathway. Reproductive Sciences, 25:609-620. https://doi.org/10.1177/1933719117734700.
11. Wang, HF. et al. 2016. Bisphenol A impairs mature sperm functions by a CatSper-relevant mechanism. Toxicological Sciences 152:145-154. https://doi.org/10.1093/toxsci/kfw070.
12. Camacho, L. et al. A two-year toxicology study of bisphenol A (BPA) in Sprague-Dawley rats: CLARITY-BPA core study results. Food and Chemical Toxicology 132:110728. https://doi.org/10.1016/j.fct.2019.110728.
13. Johnson, SA. et al. 2016. Effects of developmental exposure to bisphenol A on spatial navigational learning and memory in rats: A CLARITY-BPA study. Hormones and Behavior 80:139-148. doi:10.1016/j.yhbeh.2015.09.005.
14. Ma, L. et al. 2018. Bisphenol A promotes hyperuricemia via activating xanthine oxidase. FASEB Journal 32:1007-1016. doi:10.1096/fj.201700755R. Copy of study provided in original filing.

B) New publications and references submitted by commenters to EFSA

1. Abellan, A. et al. 2022. In utero exposure to bisphenols and asthma, wheeze, and lung function in school-age children: a prospective meta-analysis of 8 European birth cohorts. Environment International 162:107178. doi.org/10.1016/j.envint.2022.107178.

2. Dong, Y-D. et al. 2020. Abnormal differentiation of regulatory T cells and Th17 cells induced by perinatal bisphenol A exposure in female offspring mice. Molecular and Cellular Toxicology 16:167-174. https://doi.org/10.1007/s13273-019-00067-4.
3. Gao, L. et al. 2020. The imbalance of Treg/Th17 cells induced by perinatal bisphenol A exposure is associated with activation of the PI3K/Akt/mTOR signaling pathway in male offspring mice. Food and Chemical Toxicology 137:111177. https://doi.org/10.1016/j.fct.2020.111177.
4. Malaise, Y. et al. 2020a. Oral exposure to bisphenols induced food intolerance and colitis in vivo by modulating immune response in adult mice. Food and Chemical Toxicology 146:111773. https://doi.org/10.1016/j.fct.2020.111773.
5. Malaise, Y. et al. 2020b. Perinatal oral exposure to low doses of bisphenol A, S or F impairs immune functions at intestinal and systemic levels in female offspring mice. Environmental Health 19:93. https://doi.org/10.1186/s12940-020-00614-w.
6. Malaise, Y. et al. 2020c. Differential influences of the BPA, BPS and BPF on in vitro IL-17 secretion by mouse and human T cells. Toxicology in Vitro 69:104193. https://doi.org/10.1016/j.tiv.2020.104993.
7. Malaise, Y. et al. 2021. Bisphenol A, S or F mother's dermal impregnation impairs offspring immune responses in a dose and sex-specific manner in mice. Scientific Reports 11:1650. https://doi.org/10.1038/s41598-021-81231-6.
8. Wang, G. et al. 2020. Maternal vitamin D supplementation inhibits bisphenol A-induced proliferation of Th17 cells in adult offspring. Food and Chemical Toxicology 144:111604. https://doi.org/10.1016/j.fct.2020.111604.
9. Wang, G. 2022. The role of metabolism in Th17 cell differentiation and autoimmune diseases. International Immunopharmacology 103:108450. https://doi.org/10.1016/j.intimp.2021.108450.
10. Yanagisawa, R. et al. 2019. Oral exposure to low dose bisphenol A aggravates allergic airway inflammation in mice. Toxicology Reports 6:1253-1262. https://doi.org/10.1016/j.toxrep.2019.11.012.
11. Zhang, S. et al. 2021. The Alterations in and the Role of the Th17/Treg Balance in Metabolic Diseases. Frontiers in Immunology 12:678355. https://doi.org/10.3389/fimmu.2021.678355.
12. Aparicio-Soto, M. et al. 2020. TCRs with segment TRAV9-2 or a CDR3 histidine are overrepresented among nickel-specific CD4+ T cells. Allergy 75:2574-2586. https://doi.org/10.1111/all.14322.
13. Marcinkowska, E. 2020. The Vitamin D System in Humans and Mice: Similar but Not the Same. Reports 3:1. https://doi.org/10.3390/reports3010001.
14. Moreno-Cordova, V. et al. 2021. Th17 Lymphocytes in Children with Asthma: Do They Influence Control? Pediatric Allergy, Immunology, and Pulmonology 34, 4. https://doi.org/10.1089/ped.2021.0067.
15. Wildner, G. 2019. Are rats more human than mice? Immunobiology 224:172-176. https://doi.org/10.1016/j.imbio.2018.09.002.
16. Major, T.J. et al. 2018. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. BMJ 363:k3951. http://dx.doi.org/10.1136/bmj.k3951.

C) List of comments submitted to EFSA and compiled by petitioners

1. Plastics Europe Comments to EFSA on 2-22-2022 Combined.
2. American Chemical Council Comments to EFSA on 2-22-2022.
3. German Institute for Risk Assessment Comments to EFSA.
4. EFSA Comments Received Narrative – 3-28-22 (Spreadsheet).