Effects of Curcumin on Bioavailability of Dioxin-Like Pollutants in Rats

Delei Cai

Zhejiang Center for Disease Control and Prevention

Qing Chen

Zhejiang Center for Disease Control and Prevention

Jianlong Han

Zhejiang Center for Disease Control and Prevention

Yanhua Song

Zhejiang Center for Disease Control and Prevention

Zhen Meng

Zhejiang Center for Disease Control and Prevention

Yibin Zheng

Zhejiang Center for Disease Control and Prevention

Haitao Shen (✉ oldfishmann@hotmail.com)

Zhejiang Center for Disease Control and Prevention

Research Article

Keywords: Bioavailability, Curcumin, PCDD/Fs, PCBs, Rats

Posted Date: March 5th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-275821/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

In this study, we used Sprague–Dawley rats to observe the intervention effects of curcumin on bioavailability of polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (DL-PCBs). We reported the bioavailability of tetra- to hexa-chlorinated PCDD/Fs rose gradually, while that of hepta- and octa-chlorinated PCDD/Fs declined, and no obvious change was found in the bioavailability of DL-PCBs. Curcumin markedly reduced the toxic equivalent (TEQ) of PCDD/Fs in rats, illustrating it might competitively inhibit absorption of PCDD/Fs in small intestinal epithelial cells due to the similar chemical structure (diphenyl) between curcumin and PCDD/Fs. Moreover, curcumin was capable of lowering the TEQ of DL-PCBs in the liver of male rats, but caused no changes in female rats. In conclusion, the prominent decline in the bioavailability of PCDD/Fs and DL-PCBs induced by curcumin may serve as one of the detoxification mechanisms of curcumin for these pollutants.

Introduction

Polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs), also known as dioxins, and dioxin-like polychlorinated biphenyls (DL-PCBs) are typical persistent organic pollutants (POPs). The main health hazards of DL-POPs to humans are neurotoxicity, reproductive toxicity, hepatotoxicity, endocrine disruption, thyroid disruption and carcinogenicity.^[1] Much attention has been paid to the burdens of DL-POPs in the environment, food and body, as well as their toxicological effects.^[2]

Studies have elaborated that 90% of POP exposure in the human body is from dietary intake.^[3] Considering the great harm of POPs to human health, it is important to take measures to decrease the intake and accumulation of POPs and promote their excretion, thereby reducing their toxic effects. The efficacy and mechanism of bioactive extracts as an antidote to PCDD/Fs have been widely researched. For example, substances with antioxidant activity, such as docosahexaenoic acid, lycopene, ellagic acid, flavone, thymoquinone, glycyrrhiza polysaccharide and propolis have protective effects against 2,3,7,8-tetrachlorodibenzo-p-dioxin (TeCDD)-induced hepatotoxicity.^[4] *Chlorella pyrenoidosa* can facilitate the excretion of 1,2,3,4,7,8-hexachlorodibenzo-p-dioxin (HpCDD) in feces and reduce its accumulation in mouse liver.^[5] Taking in mineral oil, activated carbon and rice bran can alleviate the body burden of dioxins.^[6]

Curcumin, a natural medicine containing phenolic and quinone groups, exerts protective effects against such toxic effects as oxidative stress, humoral immunosuppression and gastric mucosal injury in rats induced by 2,3,7,8-TeCDD.^[7] It is currently believed that the detoxification mechanism of curcumin in 2,3,7,8-TeCDD is mainly realized through aryl hydrocarbon receptor (AhR)-mediated pathways.^[8] According to the analysis of curcumin homologues and quantitative structure–activity relationship, the keto-enol tautomerism of the methoxy group and β -diketone structure in curcumin is essential for inhibiting AhR transformation (Fig. 1), and adding the methyl and methoxy groups to curcumin can enhance its inhibitory effects.^[9] Nevertheless, there is another possible pathway of the detoxification

mechanism of curcumin for DL-POPs, which is not completely understood, that is, curcumin probably decreases the absorption of DL-POPs in small intestinal epithelium, and their reduced bioavailability leads to a decreased exposure concentration in organisms, thus exerting a detoxifying effect. To verify this hypothesis, rat models were applied to observe the impacts of curcumin on the bioavailability of PCDD/Fs and DL-PCBs in the liver and to explore the detoxification mechanism of curcumin for DL-POPs.

Materials And Methods

Twelve DL-PCBs and ten PCDD/Fs were purchased from AccuStandard Company [New Haven]USA. The standard substances of curcumin were provided by Zhejiang Medicine Co. Ltd. We used a PL1001-L electronic balance (Mettler Toledo) and a high-resolution gas chromatograph (HRGC) (6890N; Agilent Technologies, Palo Alto, USA) coupled with a high-resolution mass spectrometer (HRMS; Autospec Ultima; Micromass, Manchester, UK).

Clean Sprague–Dawley (SD) rats, were offered by Shanghai Laboratory Animal Co. Ltd. The protocol of this study was approved by the Animal Care Committee of Zhejiang Provincial Center for Disease Control and Prevention (ZJCDC), performed in compliance with ZJCDC Animal Care guidelines, and carried out in compliance with the ARRIVE guidelines.

The rats were raised with animal feeds bought from Zhejiang Laboratory Animal Center. The environmental conditions of testing were set as follows: barrier environment, laboratory animal use license number: SYXK (Zhejiang) 2013-0190, temperature: 20–24 °C and relative humidity 50%–70%. All the laboratory animals were fed adaptively under animal house conditions for 4 days before the experiments. Thirty-two SD rats (16 male and 16 female) were randomly divided into three groups: a control group (A), PCDD/Fs + DL-PCBs exposure group (B) and curcumin intervention group (C). The rats in each group were raised in separate cages and had free access to food and water. The rats in group B were firstly gavaged with 10 mL/kg distilled water. Next, the rats were daily administered with 5 mL/kg PCDD/Fs and DL-PCBs (diluted by soybean oil to final concentrations of 1 and 10 ng/mL, respectively) by oral gavage for 28 consecutive days. In group C, after administration of the same doses of PCDD/Fs and DL-PCBs by oral gavage, the rats were given 10 mL/kg curcumin aqueous solution (0.13 g/kg) orally for 28 consecutive days. The rats in A group were only given 5 mL/kg soybean oil and 10 mL/kg distilled water. The body weight and food intake were recorded once weekly. After the last administration, all animals were fasted overnight, anesthetized by isoflurane and killed to obtain the liver, which was stored in a -40 °C freezer for later use.

The bioavailability was calculated according to the formula:

$$BA = \frac{C \times M}{10 \times c \times V}$$

where BA is the bioavailability (%) of PCDD/Fs or DL-PCBs in the liver, C is the detected concentration (pg/g) of PCDD/Fs or DL-PCBs in the liver, M is the weight (g) of the whole liver, c is the intragastrical concentration (ng/mL) of PCDD/Fs or DL-PCBs, and V is the total intragastrical volume (mL) in 28 days.

All data were presented as mean $\pm$ standard deviation. Normality of variable distribution was verified by the Shapiro–Wilk test, with a significance level of 0.05. Student's *t*-test was adopted for comparisons of parameters between two groups, and independent-samples *t*-test was conducted for comparisons among multiple groups; $p < 0.05$ suggested that the difference was statistically significant. Calculations were performed using Excel Spread Sheet and SPSS 15.0 software.

Results

There were no significant differences in the initial body weight at 14 days, body weight at 28 days, empty body weight and liver weight of female and male rats among the A, B and C groups (ANOVA, $p > 0.05$). However, the differences in the hepatosomatic index of male rats were significant among the three groups (ANOVA, $p < 0.05$). Specifically, the hepatosomatic index of male rats was markedly higher in group B than in group A (Q test, $p < 0.05$), while it was notably lower in group C than that in group B (Q test, $p < 0.05$). No significant difference in the hepatosomatic index of female rats was observed among the three groups (ANOVA, $p > 0.05$) (Table 1). The bioavailability of WHO-PCDD/F-TEQ, WHO-DL-PCB-TEQ and total TEQ in the liver of male rats declined significantly in group C compared with group B (*t*-test, $p < 0.05$). The female rats in group C had a significantly lowered bioavailability of WHO-PCDD/F-TEQ in the liver (*t*-test, $p < 0.05$), but there were no significant changes in the bioavailability of WHO-DL-PCB-TEQ and total TEQ in female rats (*t*-test, $p > 0.05$) (Fig. 2).

Table 1

Effects of PCDD/Fs, DL-PCBs and curcumin on body weight (BW), liver weight and hepatosomatic index of rats ($\bar{x} \pm s$, g)

groups	gender	Initial BW	Medium BW	Final BW	Final empty stomach weight	Final liver weight	Hepatosomatic index (%)
A group (n = 4)	female	70.3 $\pm$ 2.6	158.0 $\pm$ 3.5	206.4 $\pm$ 3.4	183.6 $\pm$ 4.0	6.6 $\pm$ 0.4	3.6 $\pm$ 0.1
B group (n = 4)		72.5 $\pm$ 3.2	158.2 $\pm$ 7.0	206.0 $\pm$ 13.1	183.1 $\pm$ 10.3	6.8 $\pm$ 0.3	3.7 $\pm$ 0.2
C group (n = 8)		70.6 $\pm$ 1.7	154.5 $\pm$ 5.3	197.4 $\pm$ 7.7	181.3 $\pm$ 4.2	6.4 $\pm$ 0.6	3.6 $\pm$ 0.3
A group (n = 4)	male	72.4 $\pm$ 1.2	179.2 $\pm$ 13.6	288.0 $\pm$ 17.7	249.8 $\pm$ 17.7	8.8 $\pm$ 0.6	3.5 $\pm$ 0.1
B group (n = 4)		72.8 $\pm$ 1.8	182.0 $\pm$ 4.0	288.2 $\pm$ 19.6	252.0 $\pm$ 15.8	9.8 $\pm$ 1.0	3.9 $\pm$ 0.2 [#]
C group (n = 8)		71.8 $\pm$ 3.8	178.0 $\pm$ 10.8	283.8 $\pm$ 16.7	248.4 $\pm$ 17.0	9.0 $\pm$ 0.7	3.6 $\pm$ 0.1 [*]

Results expressed as mean $\pm$ standard deviation. A group: control; B group: dioxins + DL-PCBs; C group: curcumin intervention; [#] $p < 0.05$, compared to A group by Q test; ^{*} $p < 0.05$, compared to B group by Q test.

No obvious sex difference in the bioavailability of PCDD/F congeners in the liver was observed (t -test, $p > 0.05$). In comparison with group B, group C exhibited significantly decreased bioavailability of 2,3,7,8-TeCDD and 1,2,3,7,8-PeCDD in female liver as well as 2,3,7,8-TeCDF, 1,2,3,7,8-PeCDF, 2,3,7,8-TeCDD and 1,2,3,7,8-PeCDD in male liver (t -test, $p < 0.05$). The bioavailability of 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,6,7,8-HpCDD and OCDD was significantly increased in the liver of both female and male rats (t -test, $p < 0.05$). However, there were no significant changes in the bioavailability of other PCDD/Fs (t -test, $p > 0.05$). As the number of substituted chlorine atoms was increased, the bioavailability of tetra- to hexa-chlorinated PCDD/Fs rose gradually, while that of hepta- and octa-chlorinated PCDD/Fs declined. Besides, the intervention of curcumin did not alter the change patterns of the bioavailability of different PCDD/Fs (Fig. 3).

There was no obvious sex difference in the bioavailability of PCBs in rat liver (t -test, $p > 0.05$). The bioavailability of PCB169 in the liver of female rats and that of PCB156, PCB167 and PCB169 in the liver of male rats was decreased significantly in group C in contrast to group B (t -test, $p < 0.05$). The bioavailability of PCB81 and PCB123 was significantly higher in female rats (t -test, $p < 0.05$). Additionally, the changes in the bioavailability of other PCBs were not significant (t -test, $p > 0.05$). Except for the high bioavailability of PCB169 and PCB126, no apparent changes in the bioavailability were found with variations in the number of substituted chlorine atoms (4–8), and the intervention of curcumin did not alter the bioavailability change patterns of PCBs (Fig. 4).

Discussion

After exposure to 1 ng/mL PCDD/Fs and 10 ng/mL DL-PCBs, there was no significant change in the body weight and liver weight of female and male rats, or in the hepatosomatic index of female rats, whereas the hepatosomatic index of male rats was increased obviously, implying that the exposure to PCDD/Fs and DL-PCBs probably caused damage to the liver. After intervention of curcumin, the hepatosomatic index of the rats was decreased, indicating that the liver injury may have recovered. The protective effect of curcumin against liver injury has also been discovered in research on liver injury induced by carbon tetrachloride, ischemia–reperfusion, and alcohol.^[10] One study found that, as for exposure to TeCDD congeners, TeCDD toxicity is variable in different species, different strains within the same species, and different sexes within the same strain.^[11] Moreover, female Long–Evans rats are more sensitive to the acute lethality of TeCDD than males are, while male mice and guinea pigs are more sensitive to TeCDD toxicity than females are.^[12,13] In the present study, the male rats had higher sensitivity to the hepatotoxicity of POPs with a diphenyl ring, inconsistent with reports in the literature. The possible reason is that the SD rats were used as the laboratory murine strains and exposed to a low-concentration mixture (10 kinds of PCDD/Fs and 12 kinds of PCBs) for 28 days, which is different from previous studies, so the sex-dependent toxic effect may have been different.

The intervention of curcumin could have markedly decreased the bioavailability of WHO-PCDD/F-TEQ, WHO-DL-PCB-TEQ and total TEQ in the liver of male rats, but it was merely able to reduce the bioavailability of WHO-PCDD/F-TEQ in the liver of female rats, indicating that curcumin can attenuate the

bioavailability of DL-POPs. These results suggest that the decrease in the bioavailability of DL-POPs may be a detoxification mechanism of curcumin in these indicators.

Following the intervention of curcumin, the bioavailability of tetra- and penta-chlorinated PCDDs (including 2,3,7,8-TeCDD and 1,2,3,7,8-PeCDD, with a TEF of 1) and tetra- and penta-chlorinated PCDFs (including 2,3,7,8-TeCDF and 1,2,3,7,8-PeCDF, with a TEF of 0.1 and 0.03, respectively) was reduced markedly in male rats, and the impact on the bioavailability of WHO-PCDD/F-TEQ calculated based on wet weight was greater. No significant change in the bioavailability of hexa-chlorinated PCDD/F and OCDF (8Cl) was observed. The bioavailability of hepta-chlorinated PCDD/F (TEF = 0.01) and OCDD (TEF = 0.0003) was increased, which had a small influence on the bioavailability of WHO-PCDD/F-TEQ. In addition to no obvious changes in the bioavailability of tetra- to hexa-chlorinated PCDFs, variations in bioavailability of the remaining PCDD/Fs in female rats were similar to those in male rats. The bioavailability of WHO-PCDD/F-TEQ was decreased in female and male rats, illustrating that curcumin is capable of decreasing the bioavailability of PCDD/Fs. The chemical structure (diphenyl structure) of curcumin resembles that of PCDD/Fs and may competitively repress the absorption of PCDD/Fs in small intestinal epithelial cells. Nevertheless, the specific mechanism of curcumin in lowering the bioavailability of PCDD/Fs remains unclear and needs to be verified. A previous study revealed that curcumin can inhibit the absorption of other chemical substances such as cholesterol in the intestinal tract.^[14]

In female rats receiving intervention with curcumin, only the bioavailability of PCB169 (TEF = 0.03) declined prominently, while the bioavailability of PCB81 and PCB123 was increased clearly, and no obvious changes in the bioavailability of the other PCBs was observed. However, these changes were not significant, so the overall bioavailability of WHO-DL-PCB-TEQ calculated based on wet weight showed no obvious variation. Moreover, in the liver of male rats, the bioavailability of PCB156 (TEF = 0.00003), PCB167 (TEF = 0.00003) and PCB169 showed significant decreases, and the bioavailability of PCB126 (TEF = 0.1) dropped slightly but not significantly. For other PCBs, changes in bioavailability were not apparent, and the bioavailability of WHO-DL-PCB-TEQ calculated based on wet weight was reduced, implying that there is a significant sex difference in the intervention effect of curcumin on the bioavailability of PCBs. As a category of typical endocrine-disrupting chemicals with estrogen and antiandrogen effects^[15], PCBs can affect the function of the hypothalamus–pituitary (HP) axis and hinder the synthesis, metabolism and action of hormones.^[16] The decreased bioavailability of PCBs in males may be related to the functional change of the HP axis, which needs to be confirmed.

Bioavailability of PCDD/Fs and PCBs had independent change patterns along with the increase in number of chlorine atoms in the molecular structure. Specifically, the bioavailability of tetra- to hexa-chlorinated PCDD/Fs was elevated gradually, that of hepta- and octa-chlorinated PCDD/Fs was lowered, and that of PCBs displayed no obvious change patterns. Nevertheless, the change patterns of those indicators were not altered by the intervention of curcumin.

Distribution of PCDD/Fs in tissues primarily depends on the structure, chlorination level, dose range, absorption, metabolism and transport in blood of homologs.^[17] Kim *et al.* applied the quantitative

structure–property relationship method to predict the physicochemical properties of PCDD homologs^[18], and revealed that as the number of substituted chlorine atoms was increased, the water solubility of PCDDs was gradually weakened, while the octanol–water partition coefficient (K_{OW} , $\log K_{OW}$ is a substitute index of lipid–water partition coefficient) was raised gradually, indicating that highly chlorinated PCDDs are preferentially absorbed in the small intestine, and thus their bioavailability is relatively high in the liver. However, the preferential absorption law of more chlorine atoms is limited over a certain range because the organic pollutants with too high $\log K_{OW}$ and too low water solubility are not conducive to absorption by cells. Moreover, it has been found that the bioavailability of OCDD and OCDF (8Cl) in the liver and kidney fat of sheep is low.^[19] Budinsky *et al.* reported that the bioavailability of 2,3,7,8-TeCDF and 1,2,3,7,8-PeCDF is low, and that of 1,2,3,6,7,8-HxCDF is high in the rat liver, which is in line with the results of our study, but the bioavailability of 2,3,4,7,8-PeCDF was higher.^[20] Why is the bioavailability of 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF, both of which are pentachlorides, different? Kim *et al.* also demonstrated that PCDD homologs have the same number of chlorine atoms, but the substituted positions and K_{OW} are different.^[18] It may be that furans have similar conditions. Researchers have discovered that the level of PCDD/Fs in deer tissues is almost twice that in wild boar tissues, and the bioaccumulative coefficients (the ratio of the concentration in the muscle to the concentration in the environmental samples) in both deer and wild boar decrease with the increase in chlorine atom number in PCDD/F molecules.^[21] Such an accumulation mode of PCDD/F homologs differs from that in the present study, suggesting that there are differences in the absorption modes of PCDD/Fs between various species and between low-level exposure in the field and high-level exposure in the laboratory.

The pattern where there is no obvious change rule in the bioavailability of PCBs has also been reported in studies on wild boar and deer.^[21] However, Zhang *et al.* utilized loaches in rice paddy fields to investigate the bioaccumulation of organochlorine pesticides and PCBs, and discovered that the bioaccumulation was affected by environmental factors (temperature, soil, etc.), biological factors (species) and chemical factors.^[22] In the majority of bioaccumulation models, the bioaccumulation factors of organochlorine compounds are often associated with K_{OW} .^[23] When $\log K_{OW}$ is increased from 6.0 to ~ 7.0 , the bioaccumulative coefficient of PCBs increases, but the bioaccumulation factor declines conversely as $\log K_{OW}$ increases continuously. Moreover, it has been observed that PCB156 and PCB157 have the highest accumulative coefficients.^[22] It can be seen that the bioavailability may vary from species to species. There were some limitations to this study. For example, the number of animals in each group was small, and the individual differences were large, so it is difficult to obtain significant differences. Besides, the bioavailability of PCDD/Fs and PCBs was only examined in the liver, and their content in other tissues and excretion in urine and feces were not tested. Additionally, not all PCDD/Fs and PCBs were investigated; thus, the effects of curcumin on the bioavailability of PCDD/Fs and PCBs could not be assessed comprehensively. The above limitations need to be improved by subsequent studies.

Conclusion

The intervention of curcumin cannot alter the change patterns of bioavailability of various PCDD/Fs and DL-PCBs but can significantly reduce the bioavailability of WHO-PCDD/F-TEQ calculated based on wet weight in female and male rats. This illustrates that curcumin can decrease the bioavailability of PCDD/Fs and suggests that curcumin competitively inhibits the absorption of PCDD/Fs in small intestinal epithelial cells due to the similar chemical structure (diphenyl structure) between curcumin and PCDD/Fs. As a result, the bioavailability of PCDD/Fs is decreased. Furthermore, curcumin can reduce WHO-DL-PCB-TEQ, calculated from wet weight of the liver of male rats, but results in no changes in female rats. Such an apparent sex difference may be correlated with functional change of the HP axis. Curcumin can trigger evident drops in the bioavailability of PCDD/Fs and PCBs, suggesting that the decrease in the bioavailability of DL-POPs is one of the detoxification mechanisms of curcumin.

Declarations

Acknowledgments

The authors acknowledge financial support from the National Key R&D Program of China (2017YFC1600500), the Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health talents, and Science Technology Department of Zhejiang province (LGC20B050004, GD20H26001). We thank International Science Editing for editing this manuscript.

Author contributions

Cai DL and Shen HT wrote the main manuscript text and prepared all tables and figures. All authors reviewed the manuscript.

Competing interests

The author(s) declare no competing interests.

References

1. Katsoyiannis, A. & Cincinelli, A. On persistent organic pollutants in Italy - From Seveso to the Stockholm Convention and beyond. *Science of The Total Environment*. **579**, 514–516 <https://doi.org/10.1016/j.scitotenv.2016.11.067> (2017).
2. Xu, P. W. *et al.* Association of PCB, PBDE and PCDD/F body burdens with hormone levels for children in an e-waste dismantling area of Zhejiang Province, China. *Science of The Total Environment*. **499**, 55–61 <https://doi.org/10.1016/j.scitotenv.2014.08.057> (2014).
3. Shen, H. *et al.* Polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) in breast milk from Zhejiang, China. *Environment international*. **42**, 84–90 <https://doi.org/10.1016/j.envint.2011.04.004> (2012).
4. Turkez, H., Geyikoglu, F. & Yousef, M. I. Ameliorative effects of docosahexaenoic acid on the toxicity induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in cultured rat hepatocytes. *Toxicol. Ind. Health*. **32**,

- 1074–1085 <https://doi.org/10.1177/0748233714547382> (2016).
5. Takekoshi, H., Suzuki, G., Chubachi, H. & Nakano, M. Effect of *Chlorella pyrenoidosa* on fecal excretion and liver accumulation of polychlorinated dibenzo-p-dioxin in mice. *Chemosphere*. **59**, 297–304 <https://doi.org/10.1016/j.chemosphere.2004.11.026> (2005).
 6. Sallach, J. B. *et al.* Activated carbons of varying pore structure eliminate the bioavailability of 2,3,7,8-tetrachlorodibenzo-p-dioxin to a mammalian (mouse) model. *Science of The Total Environment*. **650**, 2231–2238 <https://doi.org/10.1016/j.scitotenv.2018.09.270> (2019).
 7. Ciftci, O., Tanyildizi, S. & Godekmerdan, A. Protective effect of curcumin on immune system and body weight gain on rats intoxicated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). *Immunopharmacology and Immunotoxicology*. **32**, 99–104 <https://doi.org/10.3109/08923970903164318> (2010).
 8. Choi, H. *et al.* Curcumin attenuates cytochrome P450 induction in response to 2,3,7,8-tetrachlorodibenzo-p-dioxin by ROS-dependently degrading AhR and ARNT. *Cancer Sci*. **99**, 2518–2524 <https://doi.org/10.1111/j.1349-7006.2008.00984.x> (2008).
 9. Nakai, R., Fukuda, S., Kawase, M., Yamashita, Y. & Ashida, H. Curcumin and its derivatives inhibit 2,3,7,8-tetrachloro-dibenzo-p-dioxin-induced expression of drug metabolizing enzymes through aryl hydrocarbon receptor-mediated pathway. *Bioscience Biotechnology and Biochemistry*. **82**, 616–628 <https://doi.org/10.1080/09168451.2017.1386086> (2018).
 10. Singh, N., Khullar, N., Kakkar, V. & Kaur, I. P. Attenuation of Carbon Tetrachloride-Induced Hepatic Injury with Curcumin-Loaded Solid Lipid Nanoparticles. *Biodrugs*. **28**, 297–312 <https://doi.org/10.1007/s40259-014-0086-1> (2014).
 11. Prokopec, S. D., Watson, J. D., Lee, J., Pohjanvirta, R. & Boutros, P. C. Sex-related differences in murine hepatic transcriptional and proteomic responses to TCDD. *Toxicology and applied pharmacology*. **284**, 188–196 <https://doi.org/10.1016/j.taap.2015.02.012> (2015).
 12. Pohjanvirta, R., Unkila, M., Tuomisto, J., COMPARATIVE ACUTE LETHALITY & OF 3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD), 1,2,3,7,8-PENTACHLORODIBENZO-P-DIOXIN AND 1,2,3,4,7,8-HEXACHLORODIBENZO-P-DIOXIN IN THE MOST TCDD-SUSCEPTIBLE AND THE MOST TCDD-RESISTANT RAT STRAIN. *Pharmacology & Toxicology* **73**, **2**, 52–56 <https://doi.org/10.1111/j.1600-0773.1993.tb01958.x> (1993).
 13. Enan, E., Overstreet, J. W., Matsumura, F., VandeVoort, C. A. & Lasley, B. L. Gender differences in the mechanism of dioxin toxicity in rodents and in nonhuman primates. *Reprod. Toxicol.* **10**, 401–411 [https://doi.org/10.1016/0890-6238\(96\)83995-5](https://doi.org/10.1016/0890-6238(96)83995-5) (1996).
 14. Zou, J., Zhang, S. S., Li, P. Y., Zheng, X. M. & Feng, D. Supplementation with curcumin inhibits intestinal cholesterol absorption and prevents atherosclerosis in high-fat diet-fed apolipoprotein E knockout mice. *Nutr. Res.* **56**, 32–40 <https://doi.org/10.1016/j.nutres.2018.04.017> (2018).
 15. Bell, M. R. Endocrine-disrupting actions of PCBs on brain development and social and reproductive behaviors. *Current Opinion in Pharmacology*. **19**, 134–144 <https://doi.org/10.1016/j.coph.2014.09.020> (2014).

16. Graceli, J. B. *et al.* The impact of endocrine-disrupting chemical exposure in the mammalian hypothalamic-pituitary axis. *Molecular and Cellular Endocrinology*. **518**, 110997 <https://doi.org/10.1016/j.mce.2020.110997> (2020).
17. Laurent, C., Marchand, P., Feidt, C., Le Bizec, B. & Rychen, G. Tissue distribution and bioconcentration factors of PCDD/Fs in the liver and adipose tissue following chronic ingestion of contaminated milk in rats. *Chemosphere*. **60**, 929–938 <https://doi.org/10.1016/j.chemosphere.2005.01.041> (2005).
18. Kim, M., Li, L. Y. & Grace, J. R. Predictability of physicochemical properties of polychlorinated dibenzo-p-dioxins (PCDDs) based on single-molecular descriptor models. *Environ. Pollut.* **213**, 99–111 <https://doi.org/10.1016/j.envpol.2016.02.007> (2016).
19. Hoogenboom, R. *et al.* Accumulation of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in livers of young sheep. *Chemosphere*. **122**, 137–144 <https://doi.org/10.1016/j.chemosphere.2014.11.030> (2015).
20. Budinsky, R. A. *et al.* A pilot study of oral bioavailability of dioxins and furans from contaminated soils: Impact of differential hepatic enzyme activity and species differences. *Chemosphere*. **70**, 1774–1786 <https://doi.org/10.1016/j.chemosphere.2007.08.035> (2008).
21. Warenik-Bany, M., Maszewski, S., Mikolajczyk, S. & Piskorska-Pliszczynska, J. Impact of environmental pollution on PCDD/F and PCB bioaccumulation in game animals. *Environ. Pollut.* **255**, <https://doi.org/10.1016/j.envpol.2019.113159> (2019).
22. Zhang, H. J. *et al.* Bioaccumulation of organochlorine pesticides and polychlorinated biphenyls by loaches living in rice paddy fields of Northeast China. *Environ. Pollut.* **216**, 893–901 <https://doi.org/10.1016/j.envpol.2016.06.064> (2016).
23. Costanza, J., Lynch, D. G., Boethling, R. S. & Arnot, J. A. Use of the bioaccumulation factor to screen chemicals for bioaccumulation potential. *Environmental toxicology and chemistry*. **31**, 2261–2268 <https://doi.org/10.1002/etc.1944> (2012).

Figures

Figure 1

Figure 2

Effects of curcumin on bioavailability of WHO-TEQ 2005 (* p <0.05)

Figure 3

Effects of curcumin on bioavailability of PCDDF congeners (* p <0.05)

Figure 4

Effects of curcumin on bioavailability of DL-PCB congeners (* p <0.05)