Reduction of Dioxins and Polychlorinated Biphenyls (PCBs) in Human Body

Mochida, Yoji
Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University

Fukata, Hideki
Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University

Matsuno, Yoshiharu
Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University

Mori, Chisato
Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University

https://doi.org/10.15017/4282

出版情報：福岡醫學雜誌. 98 (4), pp.106-113, 2007-04-25. 福岡医学会
バージョン：
権利関係：

Review Article

Reduction of Dioxins and Polychlorinated Biphenyls (PCBs) in Human Body

Yoji MOCHIDA, Hideki FUKATA, Yoshiharu MATSUNO and Chisato MORI

Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University, Chiba 260-8670

Abstract The accumulation of persistent lipophilic organic pollutants like dioxins and PCBs in human body is of great concern since many of these compounds may elicit adverse health effects on humans. To reduce dioxins and PCBs with long half-lives that are absorbed into the human body, we need to work actively to minimize accumulation of dioxins and PCBs taken. Lot of manner has been tested such as foods containing dietary fibers and chlorophyll, lipids (squalane etc) and anion exchange resins. Cholestyramine, a cholesterol lowering agent, was no efficacy in humans. Authors have conducted a pilot study to demonstrate the effect lowering dioxin in human bodies using colestimide. Nine patients on cdestimide for 6 months, showed mean 20% decrease respectively in both dioxin and PCB levels, and the maximum percentage decrease was approximately 40%. From a standpoint to avoid the influence on high-risk group and high-risk life stage other than next generation, the world-wide cooperation for reducing environmental chemicals is greatly appealed.

1. Exposure of Dioxins / PCBs and health hazard

The accumulation of persistent lipophilic organic pollutants like dioxins (polychlorinated dibenzofurans, polychlorinated dibenzo-p-dioxins and coplanar polychlorinated biphenyls) and PCBs (polychlorinated biphenyls) in human body is of great concern since many of these compounds may elicit adverse health effects on humans. As a representative instance of dioxin exposure to the human bodies, the citizen of Seveso City in Italy was exposed by explosion of an agrichemical factory[1]. The exposure of dioxin to human body induces contact dermatitis at early stage, and a severe case results in pustular skin necrosis. Exposure to dioxins at late stage in humans has been reported to cause skin disorders such as chloric acne and scar[1)~3)]. Imbalance of sex ratio that birth ratio of male born from a father exposed by dioxin was low has been reported as a long-term late effect by dioxin[4]. The health hazard due to extreme high exposure of PCBs and dioxins in humans have been reported as Yusho[5] in Japan and Taiwanese Yu-Cheng[6] in Taiwan. Nerve disorder, carcinogenetic action, generative dysfunction and suppression of immune system have been reported as adverse health effects to human bodies due to PCBs and dioxins[1]. On the other hand, ordinary people take mostly dioxins and PCBs from foods[7]. Adverse health effects due to a small amount of

Address for Correspondence: Chisato MORI
Department of Bioenvironmental Medicine, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan.
Fax: +81-43-226-2018
E-mail address: cmori@faculty.chiba-u.jp

dioxins and PCBs has not still been clarified. However, human fetuses are exposed to dioxins and PCBs through placenta[8]. It has been well known that the levels of dioxin and PCBs in breast milk are higher than in maternal blood[9]. As the sensitivity to chemical substances to fetuses is very high, caution should be exercised[10].

2. Pharmacodynamics of dioxins and PCBs

Dioxins and PCBs are absorbed from the digestive tract along with lipids in food due to their lipophilic nature[11]. It is generally thought that there may be two possible pathways for the excretion of xenobiotics into the gastrointestinal tract : while one is output via bile, another is direct excretion into the gastrointestinal tract without the help of bile. The excretion of dioxins and PCBs into intestine takes place mainly by the latter mechanism[12)~14)]. Dioxins and PCBs excreted into intestinal tract are partially evacuated to outside the body in the feces, however, most of them are reabsorbed in the intestine. Hence, the half-life of dioxins and PCBs in human body is depending on their isomers or residual concentrations in the body. The half-life of dioxins and PCBs is long from several years to several tens years[15]. Furthermore, it has been known that a small amount of dioxins and PCBs are also detected from sebum[16]. Breast milk is high in fat, and the concentrations of dioxins and PCBs are also high[9], these profiles have a great concern of transfer to infants from the mother.

3. Excretion of dioxins and PCBs to outside the body

To reduce dioxins and PCBs with long half-lives that are absorbed into the human body, we need to work actively to minimize accumulation of dioxins and PCBs taken. As mentioned below, diverse approaches have already been examined[17].

A. Foods products

An effect accelerating elimination of dioxins and PCBs has been confirmed to be included in plant foodstuff in animal experiments. This effect is considered to be due to dietary fiber and chlorophyll.

Various kinds of dietary fibers are included in plants. Compared to 8 kinds of crude dietary fibers derived from plants, rice bran fiber has a relatively high adsorptivity of PCBs *in vitro*. As a reason, this effect is associated with the content of lignin, the effect accelerating elimination of dioxins and PCBs was confirmed to some extent even *in vivo*[18)19)]. The diet with chitosan increased fecal excretion of Arochlor 1254 compared to the fiber-free diet[20]. The diets with fermentable fiber (polydextrose, indigestible dextrin and soy polysaccharides) increased urinary excretion of PCBs compared to the diets with water-insoluble fiber (cellulose, rice bran and chitosan)[20]. The most efficacious diets for minimizing accumulation of environmental contaminants and accelerating elimination likely include a combination of soluble and insoluble fiber, but the specific types, proportions and amounts remain to be determined[20]. Seaweed[21] abundant in dietary fiber has been also confirmed to have an effect accelerating elimination of dioxin[22].

In green vegetables[22], it appears to have high excretory effect in the vegetables such as honewort, spinach and green perilla with abundant chlorophyll. The effect accelerating elimination of dioxins and PCBs has been confirmed in the foodstuff with abundant chloro-

phyll such as Matcha[23] and Chlorella[24)~26)]. In the case of pregnant women who take Chlorella tablets, 6 g/day, for approximately 6 months, total TEQ in breast milk were approximately 30% lower in the Chlorella group than in controls[27]. According to the author's investigation, blood PCBs level in those taking barley extract equivalent to 75 mg of chlorophyll every day was lower than those not taking it[28].

B. Lipids (fat)

The effects removing PCDFs remained in the body and reducing toxicity due to squalane being an aliphatic saturated hydrocarbon were investigated using animals[13)29)30)]. In monkeys, cumulative PCDFs level in liver, kidney and heart decreased by 20-38% after squalane administration at a dose of 8 g/monkey/day for 140 days following PCDFs administration of 9 times/3 weeks at 20 (g/monkey. When liquid paraffin-mixed feed[13)31)] was given to rats, the excretion of PCDFs was promoted. Olestra[32], a non-digestible, non-absorbable dietary fat substitute, accelerated the patients' intestinal excretion of TCDDs by eight to ten fold. This is sufficient to reduce the normally observed elimination half-life of TCDDs from about 7 years to 1- 2 years[33].

C. Ion exchange resin

A mechanism of reducing dioxins and PCBs due to anion exchange resin has not sufficiently been elucidated, however, it is considered that anion exchange resin promotes excretion to outside the body by adsorbing dioxin and PCB directly or as a bile acid conjugate in digestive tract and inhibiting reabsorption of them. The effect lowering dioxins and PCBs due to cholestyramine, colestimide, DEAE cellulose[34] is being investigated.

Cholestyramine, a cholesterol lowering agent, was used to lower dioxin and PCB levels accumulated in the living body. Cholestyramine is an anion exchange resin with a structure that quaternary ammonium base is introduced into a copolymer of vinyl-benzene and styrene. The effect reducing dioxin and PCB accumulation was confirmed by cholestyramine administration alone in rats[34], however, no efficacy was observed in humans[35]. In combined administration with rice bran fiber, cholestyramine decreased PCDFs by 1.9 fold and PCBs by 2.9 fold, respectively. In case of PCBs, the excretion of PCBs could be accelerated to 2.8 fold by cholestyramine administration alone, whereas, 5.7 fold by combined administration of cholestyramine with rice bran fiber. However, since the adsorptive activation is low by cholestyramine, it has to be administered at a considerable dose. Furthermore, cholestyramine had a disadvantageous profile that it is difficult to be taken because of smelling specific to aliphatic amine.

Recently, authors have conducted a pilot study to demonstrate the effect lowering dioxins in human bodies using colestimide (INN : colestilan)[36)~38)]. Colestimide is a bland and innocuous anion exchange resin with imidazolium salt showing efficacy on hypercholesterolemia[39)~41)]. Colestimide demonstrated a higher adsorptive activation on component substance of each bile acid and lipid complex micelle (cholic acid, oleic acid, monoolein glycerol, phospholipids, cholesterol) as compared to cholestyramine[39], the effect of dioxins and PCBs elimination was therefore expected more than that of cholestyramine. Blood dioxins and PCBs levels were measured before colestimide administration and 6 months after colestimide

administration with cooperation of 10 patients on colestimide at a dose of 3 g/ day for hypercholesterolemia. Nine patients (1 patient discontinued) on colestimide for 6 months, showed mean 20% decrease respectively in both dioxins and PCBs levels, and the maximum percentage decrease was approximately 40% (Table 1, 2). The serum dioxins levels were decreased greater in patients whose dioxins levels at baseline were higher (Table 1). Percentage decrease of blood dioxins level after colestimide administration showed correlation with that of blood PCBs level (Table 2). On the other hand, in the dropouts who discontinued Colestimide administration, blood dioxins and PCBs levels increased at 6 months of administration. In the clinical study hypercholesterolemia, colestimide 3 g / day was reported to have equivalent LDL cholesterol lowering efficacy in comparison with cholestyramine 12 g/day. With regard to safety, there was smaller number of constipation and abdominal distension patients in colestimide group than that in cholestyramine group. If the excretion of dioxins and PCBs is induced by the promotion of bile acid excretion as well as in cholesterol lowering, it would be expected to be higher excretion of dioxins and PCBs in treatment with colestimide (Fig. 1a) than cholestyramine (Fig. 1b)[42].

D. Activated carbon

An effect due to activated carbon was investigated in rodents. The activated carbon showed an inhibition of PCBs absorption in intestines[34]. Also, the results for rats and guinea-pigs showed that the antidotal action of charcoal against TCDD also applies to these species[43]. At present, a research for inhibition of PCBs absorption is being conducted using an upgraded activated carbon.

Table 1 Blood level of dioxins before and after the treatment in nine subjects

	Dioxins (pg-TEQ/g-fat)		
	Before Treatment	6month Treatment	Reducation Raete
1	50	40	20%
2	19	21	−11%
3	43	36	16%
4	57	35	39%
5	20	17	15%
6	40	31	23%
7	100	74	26%
8	40	32	20%
9	27	26	4%
mean	44	35	17%
SD	25	16	14%

Table 2 Blood level of PCBs before and after the treatment in nine subjects

	PCBs (ng/g-fat)		
	Before Treatment	6month Treatment	Reducation Raete
1	240	190	21%
2	110	130	−18%
3	190	190	0%
4	360	200	44%
5	73	63	14%
6	260	230	12%
7	580	430	26%
8	360	280	22%
9	130	120	8%
mean	256	204	14%
SD	159	106	18%

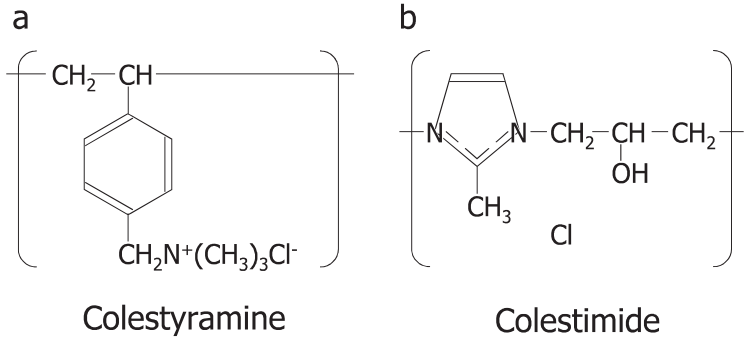

Fig. 1 structures of Colestyramine and Colestimide

4. Current situation of exposure in ordinary people (Japanese) and needs to reduce the dioxin and PCB levels in human bodies for the future generations

A high lipophilic organochemical such as dioxins and PCBs is widely detected from the human bodies. Since dioxins and PCBs levels transferred to fetuses and nursing infants reflect cumulative maternal concentrations of dioxins and PCBs, it is of great concern of influence on the next generation. To reduce chemical exposure to the next generation, it is desirable to reduce plasma organochemical concentration prior to pregnancy. For achieving this objective, the following points are important : 1) System measuring chemical concentration in the body, 2) In case the chemical concentration in the body was high, provision of the method for reducing the concentration, 3) Popularization of correct knowledge on environmental chemical concentration, 4) Working on improving the environment by overall society. From a standpoint to avoid the influence on high-risk group and high-risk life stage other than next generation, the world-wide cooperation for reducing environmental chemicals is greatly appealed.

References

1) Mocarelli P : Seveso : a teaching story. Chemosphere 43 : 391-402, 2001.
2) Caputo R, Monti M, Ermacora E, Carminati G, Gelmetti C, Gianotti R, Gianni E and Puccinelli V : Cutaneous manifestations of tetrachlorodibenzo-p-dioxin in children and adolescents. Follow-up 10 years after the Seveso, Italy, accident. J. Am. Acad. Dermatol. 19 : 812-819, 1988.
3) Mocarelli P, Needham LL, Marocchi A, Patterson DG Jr, Brambilla P, Gerthoux PM, Meazza L and Carreri V : Serum concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin and test results from selected residents of Seveso, Italy. J. Toxicol. Environ. Health 32 : 357-366, 1991.
4) Mocarelli P, Gerthoux PM, Ferrari E, Patterson DG Jr, Kieszak SM, Brambilla P, Vincoli N, Signorini S, Tramacere P, Carreri V, Sampson EJ, Turner WE and Needham LL : Paternal concentrations of dioxin and sex ratio of offspring. Lancet 355 : 1858-1863, 2000.
5] Kuratsune M, Yoshimura H, Hori Y, Okumura M, Masuda Y eds. : Yusho. Kyushu University Press, Fukuoka, Japan, 2004.
6) Guo YL, Lambert GH, Hsu CC and Hsu MM : Yucheng : health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. Int. Arch. Occup. Environ. Health 77 : 153-158, 2004.
7) Patandin S, Dagnelie PC, Mulder PG, Op de Coul E, van der Veen JE, Weisglas-Kuperus N and Sauer PJ : Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood : A comparison between breast-feeding, toddler, and long-term exposure. Environ. Health Perspect. 107 : 45-51, 1999.
8] Fukata H, Omori M, Osada H, Todaka E and Mori C : Necessity to measure PCBs and organochlorine pesticide concentrations in human umbilical cords for fetal exposure assessment. Environ. Health Perspect. 113 : 297-303, 2005.
9) Furst P : Dioxins, polychlorinated biphenyls and other organohalogen compounds in human milk. Levels, correlations, trends and exposure through breastfeeding. Mol. Nutr. Food Res. 50 : 922-33, 2006.
10) Mori C : High-risk group and high-risk life stage : Key issues in adverse effects of environmental agents on human health. Reprod. Med. Biol. 3 : 51-58, 2004.
11) Schlummer M, Moser GA, and McLachlan MS : Digestive tract absorption of PCDD/Fs, PCBs, and HCB in humans : mass balances and mechanistic considerations. Toxicol. Appl. Pharm. 152, 128-137, 1998.
12) Rohde S, Moser GA, Papke O and McLachlan MS : Clearance of PCDD/Fs via the gastrointestinal tract in occupationally exposed persons. Chemosphere 38 : 3397-3410, 1999.

13) Oguri K, Kamimura H, Koga N and Yoshimura H : Mechanisms for stimulated fecal excretion of 2,3,4,7,8-pentachlorodibenzofuran in rats by treatment with squalane and liquid paraffin. Chemosphere 16 : 1707-1712, 1987.
14) Kitamura K, Nagao M, Yamada T, Sunaga M, Hata J and Watanabe S : Dioxins in bile in relation to those in the human liver and blood. J Toxicol Sci 26 : 327-336, 2001.
15) Masuda Y : Fate of PCDF/PCB congeners and change of clinical symptoms in patients with Yusho PCB poisoning for 30 years. Chemosphere 43 : 925-930, 2001.
16) Watanabe M, Ogawa F, Katayama I and Tokusue Y : Site specific difference of PCB concentration in the skin derived sebum and collection of excreted sebum with commercial sebum-remover sheet. Fukuoka Igaku Zasshi 90 : 154-156, 1999. (in Japanese)
17) Kamimura H and Yoshimura H : Stimulation of fecal excretion of the etiological compounds of yusho in rats. Fukuoka Igaku Zasshi 78 : 266-280, 1987. (in Japanese)
18) Takenaka S, Moria K and Takahashi K : Stimulation of the fecal excretion of polychlorinated biphenyls (KC-600) by diets containing rice bran fiber and cholestyramine. Fukuoka Igaku Zasshi 82 : 310-316, 1991. (in Japanese)
19) Morita K, Hirakawa H, Matsueda T, Iida T and Tokiwa H : Stimulating effect of dietary fiber on fecal excretion of polychlorinated dibenzofurans (PCDF) and polychlorinated dibenzo-p-dioxins (PCDD) in rats. Fukuoka Igaku Zasshi 84 : 273-281, 1993. (in Japanese)
20) Kimura Y, Nagata Y and Buddington RK : Some dietary fibers increase elimination of orally administered polychlorinated biphenyls but not that of retinol in mice. J. Nutr. 34 : 135-142, 2004.
21) Morita K and Nakano T : Seaweed accelerates the excretion of dioxin stored in rats. J. Agric. Food Chem. 50 : 910-917, 2002.
22) Morita K, Matsueda T and Iida T : Effect of green vegetable on digestive tract absorption of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans in rats. Fukuoka Igaku Zasshi 90 : 171-83, 1999. (in Japanese)
23) Morita K, Matsueda T and Iida T : Effect of green tea (matcha) on gastrointestinal tract absorption of polychlorinated biphenyls, polychlorinated dibenzofurans and polychlorinated dibenzo-p-dioxins in rats. Fukuoka Igaku Zasshi 88 : 162-168, 1997. (in Japanese)
24] Morita K, Ogata M and Hasegawa T : Chlorophyll derived from Chlorella inhibits dioxin absorption from the gastrointestinal tract and accelerates dioxin excretion in rats. Environ Health Perspect. 109 : 289-294, 2001.
25) Morita K, Matsueda T, Iida T and Hasegawa T : Chlorella accelerates dioxin excretion in rats. J. Nutr. 129 : 1731-1736, 1999.
26) Takekoshi H, Suzuki G, Chubachi H and Nakano M : Effect of Chlorella pyrenoidosa on fecal excretion and liver accumulation of polychlorinated dibenzo-p-dioxin in mice. Chemosphere 59 : 297-304, 2005.
27) Nakano S, Noguchi T, Takekoshi H, Suzuki G and Nakano M : Maternal-fetal distribution and transfer of dioxins in pregnant women in Japan, and attempts to reduce maternal transfer with Chlorella (Chlorella pyrenoidosa) supplements. Chemosphere 61 : 1244-1255, 2005.
28) Fukata H, Aotsuka Y, Ueyama H and Mori C : Current status of blood PCB levels of Japanese people and it's reduction using barley extract. Pharmac. Soc Jpn 42 : P29 [S] am-402, 2006.
29) Yoshimura H, Kamimura H, Oguri K and Saeki S : Stimulating effect of squalane on fecal excretion of a high toxic 2,3,7,8-pentachlorodibenzofran (PenCDF) in rats. Fukuoka Igaku Zasshi 76 : 184-189, 1985. (in Japanese)
30) Hori S, Obana H and Kashimoto T : Studies on therapeutic effect of squalane on symptoms of PCDFs poisoning in monkeys. Fukuoka Igaku Zasshi 78 : 281-285, 1987.
31) Kamimura H, Naganuma T, Oguri K and Yoshimura H : Stimulating effect of liquid paraffin and cholestyramine on fecal excretion on 2,3,4,7,8-pentachlorodibenzofuran in rats. Eisei Kagaku 32 : P-19, 1986.
32) Moser GA and McLachlan MS : A non-absorbable dietary fat substitute enhances elimination of persistent lipophilic contaminants in humans. Chemosphere 39 : 1513-1521, 1999.
33) Geusau A, Tschachler E, Meixner M, Sandermann S, Papke O, Wolf C, Valic E and Stingl G,

McLachlan M : Olestra increases faecal excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Lancet 354 : 1266-1267, 1999.
34) Araki Y : Influences of charcoal and other drugs on the intestinal absorption of PCB. Fukuoka Igaku Zasshi 65 : 58-60, 1974.
35) Iida T, Hirakawa H, Matsueda T, Nakagawa R, Takenaka S, Morita K, Narazaki Y, Fukamachi K, Tokiwa H and Takahashi K : Therapeutic trial for promotion of fecal excretion of PCDFs and PCBs by the administration of cholestyramine in Yusho patients. Fukuoka Igaku Zasshi 82 : 317-325, 1987.
36) Sakurai K, Todaka E, Saito Y and Mori C : Pilot study to reduce dioxins in the human body. Intern Med 43, 792-795, 2004.
37】 Sakurai Y, Fukata, H., Todaka, E., Bujo, H., Saito, Y. and Mori, C : Colestimide reduces blood polychlorinated bipheny (PCB) levels. Intern. Med. 45 : 327-328, 2006.
38) Fukata H, Sakurai K, Matsuno Y, Mochida Y, Komiyama M, Todaka E, Bujo H, Saito Y and Mori C : Pilot study on reducing dioxins and polychlorinated biphenyls in the human body. Jpn J. Chin. Ecol. 15 : 35-40, 2006. (in Japanese)
39】 Shimada H, Mitsuka M and Umezu K : The interaction between MCI-196 and bile acid or other biological substances. Comparison with chlolestyramine. Jpn Pharmacol. Ther. 24, 127-132, 1996. (in Japanese)
40) Matsuzaki Y : Colestimide : the efficacy of a novel anion-exchange resin in cholestatic disorders. J. Gastroenterol. Hepatol. 17 : 1133-1135, 2002.
41) Onishi T, Sano N and Takikawa H : J Gastroenterol. Hepatol. 17 : 697-701, 2002.
42】 MCI-196 Study Group : J. Clin. Ther. Med., 12, 1641-1692, 1996.
43) Manara L, Coccia P and Croci T : Prevention of TCDD toxicity in laboratory rodents by addition of charcoal or cholic acids to chow. Food Chem. Toxicol. 22 : 815-818, 1984.

(References with numbers in bold are listed as important ones for readers.)

（和文抄録）

人体中のダイオキシンや PCB の削減

千葉大学大学院 医学研究院 環境生命医学

持 田 陽 司，深 田 秀 樹，松 野 義 晴，森 千 里

ダイオキシンや PCB 等の脂溶性の高い化学物質は，生体内での蓄積性が高く，生体に悪影響を及ぼす恐れがある．感受性の高い未来世代や高曝露者の有機有害物質レベルを減少させる方法を確立することが必要である．ダイオキシンや PCB は腸管から体内への吸収と排泄が繰り返されるため半減期が長いので，これらの体内濃度を減らすためには，積極的に低減させる必要がある．食物繊維や葉緑素を多く含む食品類，スクワラン等の油脂類，陰イオン交換樹脂，活性炭等によるものが報告されている．医薬品ではコレスチラミンが検討されたが，十分な効果が得られなかった．最近，著者らは少数例ではあるがコレスチミドを用いた人体におけるダイオキシン低下効果のパイロット試験について報告した．コレスチミドの 6 ケ月の服用で，最大で 40％，平均 20％の低減効果があった．化学物質曝露による次世代へのリスクを軽減するために，ハイリスク群及びハイリスクライフステージの観点を取り入れ，ワールドワイドな協力による総合的な取り組みが求められている．