stimulation for 18 months and the related factors [in Japanese]. Jpn J Publ Health 44:346-352.
3. Aris A. 2014. Estimation of bisphenol A (BPA) concentrations in pregnant women, fetuses and nonpregnant women in Eastern Townships of Canada. Reprod Toxicol 45:8-13.
4. Bayley N. 1993. Manual for the Bayley Scales of Infant Development. 2nd ed. New York: Phsycological Corporation.
5. Bellinger DC, Trachtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S. 2007. A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: The new england children's amalgam trial. Journal of the American Dental Association (1939) 138:1210-1216.
6. Bellinger DC, Trachtenberg F, Zhang A, Tavares M, Daniel D, McKinlay S. 2008. Dental amalgam and psychosocial status: The new england children's amalgam trial. Journal of dental research 87:470-474.
7. Biedermann S, Tschudin P, Grob K. 2010. Transfer of bisphenol a from thermal printer paper to the skin. Analytical and bioanalytical chemistry 398:571-576.
8. Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, et al. 2009. Prenatal bisphenol a exposure and early childhood behavior. Environmental health perspectives 117:1945-1952.
9. Braun JM, Kalkbrenner AE, Calafat AM, Bernert JT, Ye X, Silva MJ, et al. 2011. Variability and predictors of urinary bisphenol a concentrations during pregnancy. Environmental health perspectives 119:131-137.
10. Braun JM, Kalkbrenner AE, Just AC, Yolton K, Calafat AM, Sjodin A, et al. 2014. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: The home study. Environmental health perspectives 122:513-520.
11. Brucker-Davis F, Ferrari P, Boda-Buccino M, Wagner-Mahler K, Pacini P, Gal J, Azuar P, Fenichel P. 2011. Cord blood thyroid tests in boys born with and without cryptorchidism: correlations with birth parameters and in utero xenobiotics exposure. Thyroid 21(10):1133-41.
12. Chevrier J, Gunier RB, Bradman A, Holland NT, Calafat AM, Eskenazi B, Harley KG. 2013. Maternal urinary bisphenol a during pregnancy and maternal and neonatal thyroid function in the CHAMACOS study. Environ Health Perspect 121(1):138-44.
13. Chou WC, Chen JL, Lin CF, Chen YC, Shih FC, Chuang CY. 2011. Biomonitoring of bisphenol A concentrations in maternal and

umbilical cord blood in regard to birth outcomes and adipokine expression: a birth cohort study in Taiwan. Environ Health 10:94.

14. Cox KH, Gatewood JD, Howeth C, Rissman EF. 2010. Gestational exposure to bisphenol a and cross-fostering affect behaviors in juvenile mice. Hormones and behavior 58:754-761.
15. Funabashi T, Kawaguchi M, Furuta M, Fukushima A, Kimura F. 2004. Exposure to bisphenol A during gestation and lactation causes loss of sex difference in corticotropin-releasing hormone-immunoreactive neurons in the bed nucleus of the stria terminalis of rats. Psychoneuroendocrinology 29(4):475-85.
16. Geens T, Goeyens L, Covaci A. 2011. Are potential sources for human exposure to bisphenol-a overlooked? International journal of hygiene and environmental health 214:339-347.
17. Harley KG, Gunier RB, Kogut K, Johnson C, Bradman A, Calafat AM, et al. 2013. Prenatal and early childhood bisphenol a concentrations and behavior in school-aged children. Environmental research 126:43-50.
18. Huang PC, Kuo PL, Chou YY, Lin SJ, Lee CC. 2009. Association between prenatal exposure to phthalates and the health of newborns. Environment international 35:14-20.
19. Hurst CH, Waxman DJ. 2003. Activation of pparalpha and ppargamma by environmental phthalate monoesters. Toxicological sciences : an official journal of the Society of Toxicology 74:297-308.
20. Ito Y, Yokota H, Wang R, Yamanoshita O, Ichihara G, Wang H, et al. 2005. Species differences in the metabolism of di(2-ethylhexyl) phthalate (dehp) in several organs of mice, rats, and marmosets. Archives of toxicology 79:147-154.
21. Jurewicz J, Hanke W. 2011. Exposure to phthalates: Reproductive outcome and children health. A review of epidemiological studies. International journal of occupational medicine and environmental health 24:115-141.
22. Kaneko M, Okada R, Yamamoto K, Nakamura M, Mosconi G, Polzonetti-Magni AM, Kikuyama S. 2008. Bisphenol A acts differently from and independently of thyroid hormone in suppressing thyrotropin release from the bullfrog pituitary. Gen Comp Endocrinol 155(3):574-80.
23. Kato K, Silva MJ, Brock JW, Reidy JA, Malek NA, Hodge CC, et al. 2003. Quantitative detection of nine phthalate metabolites in human serum using reversed-phase high-performance liquid

chromatography-electrospray ionization-tandem mass spectrometry. Journal of analytical toxicology 27:284-289.

24. Kim BN, Cho SC, Kim Y, Shin MS, Yoo HJ, Kim JW, et al. 2009. Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. Biological psychiatry 66:958-963.
25. Kishi R, Sasaki S, Yoshioka E, Yuasa M, Sata F, Saijo Y, et al. 2011. Cohort profile: The hokkaido study on environment and children's health in japan. International journal of epidemiology 40:611-618.
26. Kishi R, Kobayashi S, Ikeno T, Araki A, Miyashita C, Itoh S, et al. 2013. Ten years of progress in the hokkaido birth cohort study on environment and children's health: Cohort profile--updated 2013. Environmental health and preventive medicine 18:429-450.
27. Koch HM, Rossbach B, Drexler H, Angerer J. 2003. Internal exposure of the general population to dehp and other phthalates--determination of secondary and primary phthalate monoester metabolites in urine. Environmental research 93:177-185.
28. Koch HM, Preuss R, Angerer J. 2006. Di(2-ethylhexyl)phthalate (dehp): Human metabolism and internal exposure-- an update and latest results. International journal of andrology 29:155-165; discussion 181-155.
29. Kosarac I, Kubwabo C, Lalonde K, Foster W. 2012. A novel method for the quantitative determination of free and conjugated bisphenol A in human maternal and umbilical cord blood serum using a two-step solid phase extraction and gas chromatography/tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 898:90-4.
30. Kundakovic M, Gudsnuk K, Franks B, Madrid J, Miller RL, Perera FP, Champagne FA. 2013. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. Proc Natl Acad Sci U S A 110(24):9956-61.
31. Kuwahara R, Kawaguchi S, Kohara Y, Cui H, Yamashita K. 2013. Perinatal exposure to low-dose bisphenol a impairs spatial learning and memory in male rats. Journal of pharmacological sciences 123:132-139.
32. Lampen A, Zimnik S, Nau H. 2003. Teratogenic phthalate esters and metabolites activate the nuclear receptors ppars and induce differentiation of f9 cells. Toxicology and applied pharmacology 188:14-23.
33. Lee HJ, Chattopadhyay S, Gong EY, Ahn RS, Lee K. 2003.

Antiandrogenic effects of bisphenol a and nonylphenol on the function of androgen receptor. Toxicological sciences : an official journal of the Society of Toxicology 75:40-46.

34. Lee YJ, Ryu HY, Kim HK, Min CS, Lee JH, Kim E, Nam BH, Park JH, Jung JY, Jang DD, Park EY, Lee KH, Ma JY, Won HS, Im MW, Leem JH, Hong YC, Yoon HS. 2008. Maternal and fetal exposure to bisphenol A in Korea. Reprod Toxicol 25(4):413-9.
35. Leranth C, Szigeti-Buck K, Maclusky NJ, Hajszan T. 2008. Bisphenol A prevents the synaptogenic response to testosterone in the brain of adult male rats. Endocrinology 149(3):988-94.
36. Lester B, Tronick E. 2004. Using the NNNS TM. NICU Network Neurobehavioral Scale (NNNS) manual. 13.
37. Li AA, Baum MJ, McIntosh LJ, Day M, Liu F, Gray LE, Jr. 2008. Building a scientific framework for studying hormonal effects on behavior and on the development of the sexually dimorphic nervous system. Neurotoxicology 29:504-519.
38. Li Y, Zhuang M, Li T, Shi N. 2009. Neurobehavioral toxicity study of dibutyl phthalate on rats following in utero and lactational exposure. Journal of applied toxicology : JAT 29:603-611.
39. MacLusky NJ, Hajszan T, Leranth C. 2005. The environmental estrogen bisphenol a inhibits estradiol-induced hippocampal synaptogenesis. Environ Health Perspect. 2005 113(6):675-9.
40. Manson JE. 2008. Prenatal exposure to sex steroid hormones and behavioral/cognitive outcomes. Metabolism 57 (suppl 2), S16-21.
41. Lin S, Ku HY, Su PH, Chen JW, Huang PC, Angerer J, et al. 2011. Phthalate exposure in pregnant women and their children in central taiwan. Chemosphere 82:947-955.
42. Maserejian NN, Trachtenberg FL, Hauser R, McKinlay S, Shrader P, Bellinger DC. 2012. Dental composite restorations and neuropsychological development in children: Treatment level analysis from a randomized clinical trial. Neurotoxicology 33:1291-1297.
43. Meeker JD, Calafat AM, Hauser R. 2010. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environ Sci Techno 44(4):1458-63.
44. Meeker JD, Ferguson KK. 2011. Relationship between urinary phthalate and bisphenol a concentrations and serum thyroid measures in u.S. Adults and adolescents from the national health and nutrition examination survey (nhanes) 2007-2008. Environmental

health perspectives 119:1396-1402.
45. Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, et al. 2011. Endocrine disruptors and childhood social impairment. Neurotoxicology 32:261-267.
46. Naciff JM, Jump ML, Torontali SM, Carr GJ, Tiesman JP, Overmann GJ, et al. 2002. Gene expression profile induced by 17alpha-ethynyl estradiol, bisphenol a, and genistein in the developing female reproductive system of the rat. Toxicological sciences : an official journal of the Society of Toxicology 68:184-199.
47. Nakajima S, Saijo Y, Kato S, Sasaki S, Uno A, Kanagami N, Hirakawa H, Hori T, Tobiishi K, Todaka T, Nakamura Y, Yanagiya S, Sengoku Y, Iida T, Sata F, Kishi R.
48. Effects of prenatal exposure to polychlorinated biphenyls and dioxins on mental and motor development in Japanese children at 6 months of age. 2006. Environ Health Perspect 114(5):773-8.Nakamura K, Itoh K, Yaoi T, Fujiwara Y, Sugimoto T, Fushiki S. 2006. Murine neocortical histogenesis is perturbed by prenatal exposure to low doses of Bisphenol A. J Neurosci Res 84(6):1197-205.
49. Nakamura K, Itoh K, Sugimoto T, Fushiki S. 2007. Prenatal exposure to bisphenol A affects adult murine neocortical structure. Neurosci Lett. 420(2):100-5.
50. Patisaul HB, Fortino AE, Polston EK. 2006. Neonatal genistein or bisphenol-a exposure alters sexual differentiation of the avpv. Neurotoxicology and teratology 28:111-118.
51. Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, Rauh V, et al. 2012. Prenatal bisphenol a exposure and child behavior in an inner-city cohort. Environmental health perspectives 120:1190-1194.
52. Poimenova A, Markaki E, Rahiotis C, Kitraki E. 2010. Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol a. Neuroscience 167:741-749.
53. Reynolds CR, Kamphaus RW. 2004. BASC-2: Behavior Assessment System for Children, Second edition Manual AGS Publishing, Circle Pines, NM.
54. Romero-Franco M, Hernandez-Ramirez RU, Calafat AM, Cebrian ME, Needham LL, Teitelbaum S, et al. 2011. Personal care product use and urinary levels of phthalate metabolites in mexican women. Environment international 37:867-871.
55. Rubin BS, Lenkowski JR, Schaeberle CM, Vandenberg LN, Ronsheim PM,

Soto AM. 2006. Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol a. Endocrinology 147:3681-3691.

56. Suzuki Y, Niwa M, Yoshinaga J, Watanabe C, Mizumoto Y, Serizawa S, et al. 2009. Exposure assessment of phthalate esters in japanese pregnant women by using urinary metabolite analysis. Environmental health and preventive medicine 14:180-187.
57. Tanaka T. 2005. Reproductive and neurobehavioural effects of bis(2-ethylhexyl) phthalate (dehp) in a cross-mating toxicity study of mice. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 43:581-589.
58. Tanida T, Warita K, Ishihara K, Fukui S, Mitsuhashi T, Sugawara T, Tabuchi Y, Nanmori T, Qi WM, Inamoto T, Yokoyama T, Kitagawa H, Hoshi N. 2009. Fetal and neonatal exposure to three typical environmental chemicals with different mechanisms of action: mixed exposure to phenol, phthalate, and dioxin cancels the effects of sole exposure on mouse midbrain dopaminergic nuclei. Toxicol Lett. 189(1):40-7.
59. Tando S, Itoh K, Yaoi T, Ikeda J, Fujiwara Y, Fushiki S. 2007. Effects of pre- and neonatal exposure to bisphenol A on murine brain development. Brain Dev 29(6):352-6.
60. Tang WY, Morey LM, Cheung YY, Birch L, Prins GS, Ho SM. 2012. Neonatal exposure to estradiol/bisphenol A alters promoter methylation and expression of Nsbp1 and Hpcal1 genes and transcriptional programs of Dnmt3a/b and Mbd2/4 in the rat prostate gland throughout life. Endocrinology 153(1):42-55.
61. Tellez-Rojo MM, Cantoral A, Cantonwine DE, Schnaas L, Peterson K, Hu H, et al. 2013. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. The Science of the total environment 461-462:386-390.
62. Tian YH, Baek JH, Lee SY, Jang CG. 2010. Prenatal and postnatal exposure to bisphenol a induces anxiolytic behaviors and cognitive deficits in mice. Synapse (New York, NY) 64:432-439.
63. Vandenberg LN, Maffini MV, Sonnenschein C, Rubin BS, Soto AM. 2009. Bisphenol-a and the great divide: A review of controversies in the field of endocrine disruption. Endocrine

reviews 30:75-95.

64. Viberg H, Lee I. 2012. A single exposure to bisphenol a alters the levels of important neuroproteins in adult male and female mice. Neurotoxicology 33:1390-1395.
65. Wang F, Hua J, Chen M, Xia Y, Zhang Q, Zhao R, Zhou W, Zhang Z, Wang B. 2012. High urinary bisphenol A concentrations in workers and possible laboratory abnormalities. Occup Environ Med 69(9):679-84.
66. Wang T, Lu J, Xu M, Xu Y, Li M, Liu Y, Tian X, Chen Y, Dai M, Wang W, Lai S, Bi Y, Ning G. 2013. Urinary bisphenol a concentration and thyroid function in Chinese adults. Epidemiology 24(2):295-302.
67. Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, et al. 2007. In vitro molecular mechanisms of bisphenol a action. Reproductive toxicology (Elmsford, NY) 24:178-198.
68. Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, Hoepner L, et al. 2012. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environmental health perspectives 120:290-295.
69. Wittassek M, Angerer J. 2008. Phthalates: Metabolism and exposure. International journal of andrology 31:131-138.
70. Wittassek M, Angerer J, Kolossa-Gehring M, Schafer SD, Klockenbusch W, Dobler L, et al. 2009. Fetal exposure to phthalates--a pilot study. International journal of hygiene and environmental health 212:492-498.
71. Wolstenholme JT, Taylor JA, Shetty SR, Edwards M, Connelly JJ, Rissman EF. 2011. Gestational exposure to low dose bisphenol a alters social behavior in juvenile mice. PloS one 6:e25448.
72. Wormuth M, Scheringer M, Vollenweider M, Hungerbuhler K. 2006. What are the sources of exposure to eight frequently used phthalic acid esters in europeans? Risk analysis : an official publication of the Society for Risk Analysis 26:803-824.
73. Xu XH, Zhang J, Wang YM, Ye YP, Luo QQ. 2010. Perinatal exposure to bisphenol-a impairs learning-memory by concomitant down-regulation of n-methyl-d-aspartate receptors of hippocampus in male offspring mice. Hormones and behavior 58:326-333.Xu X, Tian D, Hong X, Chen L, Xie L. 2011. Sex-specific influence of exposure to bisphenol-a between adolescence and young adulthood on mouse behaviors. Neuropharmacology 61:565-573.
74. Xu X, Hong X, Xie L, Li T, Yang Y,

Zhang Q, et al. 2012. Gestational and lactational exposure to bisphenol-a affects anxiety- and depression-like behaviors in mice. Hormones and behavior 62:480-490.

75. Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J. 2011. Prenatal exposure to bisphenol a and phthalates and infant neurobehavior. Neurotoxicology and teratology 33:558-566.
76. Zhang T, Sun H, Kannan K. 2013. Blood and urinary bisphenol A concentrations in children, adults, and pregnant women from china: partitioning between blood and urine and maternal and fetal cord blood. Environ Sci Technol 7(9):4686-94.
77. Zoeller RT, Bansal R, Parris C. 2005. Bisphenol-a, an environmental contaminant that acts as a thyroid hormone receptor antagonist in vitro, increases serum thyroxine, and alters rc3/neurogranin expression in the developing rat brain. Endocrinology 146:607-612.

Table 1. Parental and child basic characteristics (N = 121).

Parental characteristics		Mean ± S.D. or median (IQR) or number (%)
Maternal age (years)		30.9 ± 4.8
Maternal education	≦ 12 years	47 (38.8)
	> 12 years	74 (61.2)
Paternal age (years)		32.7 ± 5.9
Paternal education	≦ 12 years	37 (30.6)
	> 12 years	84 (69.4)
Family income	< 5M yen	76 (62.8)
	≧ 5M yen	45 (37.2)
Maternal working during pregnancy	Yes	12 (9.9)
	No	109 (90.1)
Maternal smoking during pregnancy	Yes	13 (10.7)
	No	108 (89.3)
Maternal prepregnancy BMI (kg/m^2)		20.9 ± 2.6
Parity	0	69 (57.0)
	1	38 (31.4)
	≧ 2	14 (11.6)
Caffeine intake during pregnancy (mg/day)		120.75 (66.75-183.50)
Alcohol consumption during pregnancy	Yes	41 (33.9)
	No	80 (66.1)
Child characteristics		
Sex	Male	53 (43.8)
	Female	68 (56.2)
Birth weight (g)		3158 ± 316
Birth length (cm)		48.5 ± 1.5
Gestational age (days)		278.5 ± 7.1
Duration of breast feeding*	< 3 months	8 (6.6)
	≧ 3 months	71 (58.7)
	Data missing	42 (34.7)

* Duration of breast feeding was obtained from questionnaire at 18 month old.
** Maximum score is 30. *** Maximum score is 38.

Table 2. Characteristics of exposure and outcomes.

Characteristics	Mean ± S.D. or median (IQR) or number (%)
Cord blood BPA level (ng/ml)	0.050 (LOD-0.076)
BSID-II MDI @ 6 month	90.7 (5.9)
BSID-II PDI @ 6 month	90.4 (11.0)
HOME score @ 6 month**	22.8 (2.6)
BSID-II MDI @ 18 month (N = 86)	83.3 (11.7)
BSID-II PDI @ 18 month (N = 86)	88.0 (12.0)
HOME score @ 18 month*** (N = 89)	28.0 (3.7)
TSH (μU/ml)	1.90 (1.10-3.20)
FT4 (ng/ml)	2.00 (1.80-2.25)

Table 3. BPA levels and MDI, PDI scores at 6 and 18 months in relation to participants' characteristics.

		BPA levels		MDI at 6 month		PDI at 6 month		MDI at 18 month		PDI at 18 month	
Parental characteristics		mean (S.D)	p-value	mean (S.D)	p-value	mean (S.D)	p-value	mean (S.D)	p-value	mean (S.D)	p-value
Maternal age (years)		ρ = -0.110	0.230	ρ = 0.098	0.284	ρ = -0.064	0.484	ρ = -0.019	0.863	ρ = -0.060	0.582
Paternal age (years)		ρ = -0.097	0.289	ρ = 0.112	0.221	ρ = -0.153	0.093	ρ = 0.001	0.993	ρ = -0.075	0.494
Maternal Education	**≦ 12 years**	0.057 (0.036)	0.578	91.2 (4.4)	0.472	90.9 (10.1)	0.722	83.2 (13.2)	0.978	86.1 (12.3)	0.252
	> 12 years	0.053 (0.036)		90.5 (6.7)		90.2 (11.6)		83.3 (10.8)		89.2 (12.7)	
Paternal Education	**≦ 12 years**	0.061 (0.043)	0.194	89.7 (5.9)	0.201	90.6 (11.4)	0.908	79.6 (11.4)	0.071	83.8 (11.6)	0.043*
	> 12 years	0.052 (0.033)		91.2 (5.9)		90.4 (10.8)		84.7 (11.6)		89.6 (11.8)	
Family income	**< 5M yen**	0.058 (0.040)	0.153	90.6 (6.1)	0.693	90.8 (11.3)	0.632	81.2 (11.3)	0.043*	87.1 (12.6)	0.388
	≧ 5M yen	0.049 (0.028)		91.0 (5.6)		89.8 (10.4)		86.3 (11.8)		89.3 (11.1)	
Maternal working during pregnancy	**Yes**	0.042 (0.033)	0.183	90.5 (5.9)	0.218	87.8 (11.5)	0.386	82.5 (10.7)	0.867	90.7 (10.4)	0.573
	No	0.056 (0.036)		92.7 (6.2)		90.7 (10.9)		83.3 (11.8)		87.8 (12.0)	
Maternal smoking during pregnancy	**Yes**	0.064 (0.031)	0.311	89.0 (7.1)	0.263	87.2 (10.6)	0.265	79.5 (8.9)	0.415	84.0 (10.4)	0.401
	No	0.054 (0.037)		91.0 (5.8)		90.8 (11.0)		83.6 (11.9)		88.3 (12.1)	
Parity	**0**	0.056 (0.035)	0.831	90.8 (5.8)	0.324	90.4 (11.8)	0.876	81.6 (12.4)	0.124	86.9 (12.1)	0.071
	1	0.056 (0.041)		89.7 (6.5)		90.3 (9.5)		86.9 (10.4)		87.2 (11.8)	
	≧ 2	0.048 (0.029)		93.0 (4.6)		90.8 (11.3)		80.2 (10.1)		96.4 (9.5)	
Caffeine intake during pregnancy (mg/day)		ρ = 0.028	0.759	ρ = -0.093	0.310	ρ = -0.230	0.011*	ρ = 0.008	0.938	ρ = -0.071	0.518
Alcohol consumption during pregnancy	**Yes**	0.053 (0.034)	0.636	90.6 (6.0)	0.885	91.4 (10.6)	0.500	83.9 (9.9)	0.704	89.6 (11.3)	0.352
	No	0.056 (0.037)		90.8 (5.9)		90.0 (11.2)		82.9 (12.7)		87.1 (12.4)	
Child characteristics											
Sex	**Male**	0.055 (0.030)	0.856	91.4 (5.5)	0.273	90.2 (9.4)	0.815	79.4 (11.3)	0.005	84.0 (10.9)	0.006*
	Female	0.054 (0.041)		90.2 (6.2)		90.6 (12.1)		86.4 (11.2)		91.1 (12.0)	
Birth weight (g)		ρ = 0.127	0.164	ρ = 0.063	0.491	ρ = 0.075	0.415	ρ = -0.037	0.737	ρ = 0.089	0.417
Birth length (cm)		ρ = 0.063	0.492	ρ = 0.009	0.918	ρ = 0.112	0.220	ρ = -0.039	0.720	ρ = -0.005	0.966
Gestational age (days)		ρ = 0.025	0.787	ρ = 0.125	0.170	ρ = 0.087	0.345	ρ = 0.209	0.053	ρ = 0.105	0.334
Duration of breast feeding*	**< 3 months**	0.042 (0.026)	0.229	90.3 (3.5)	0.879	95.4 (13.8)	0.250	80.0 (3.9)	0.123	88.7 (9.7)	0.760
	≧ 3 months	0.059 (0.039)		90.6 (6.5)		90.8 (10.3)		83.7 (11.8)		87.1 (12.4)	
HOME scale @ 6 month**		ρ = -0.009	0.822	ρ = 0.005	0.953	ρ = -0.030	0.747				
HOME scale @ 18 month***		ρ = -0.072	0.502					ρ = 0.201	0.072	ρ = 0.201	0.072

* Duration of breast feeding was determined from questionnaire at 18 month old.
** Maximum score is 30. *** Maximum score is 38.

Table 4. Association between natural log transformed TSH, FT4 levels at birth and natural log transformed cord blood BPA concentration (N=121).

	TSH		FT4	
	Adjusted[a] β (95%CI)	p-value	Adjusted[a] β (95%CI)	p-value
All	-0.15 (-0.38, 0.08)	0.206	0.03 (-0.02, 0.08)	0.289
Male	0.05 (-0.38, 0.48)	0.823	0.04 (-0.05, 0.12)	0.409
Female	-0.23 (-0.50, 0.04)	0.089	0.02 (-0.05, 0.09)	0.491

[a] Adjusted for child's age (days) at hormone measurement.

Table 5. Association between BSID-II (MDI, PDI) at 6 month and natural log transformed cord blood BPA concentration (N=121).

	Crude		Adjusted[a]	
All	β	p-value	β	p-value
MDI @ 6 month	-0.56 (-2.26, 1.15)	0.521	-0.65 (-2.39, 1.05)	0.463
PDI @ 6 month	-1.37 (-4.53, 1.78)	0.390	-1.50 (-4.71, 1.71)	0.357
Male	β	p-value	β	p-value
MDI @ 6 month	1.52 (-1.15, 4.20)	0.258	1.38 (-1.40, 4.16)	0.323
PDI @ 6 month	-2.19 (-6.72, 2.34)	0.336	-3.18 (-7.70, 1.35)	0.164
Female	β	p-value	β	p-value
MDI @ 6 month	-1.87 (-4.11, 0.36)	0.099	-1.99 (-4.28, 0.31)	0.088
PDI @ 6 month	-0.87 (-5.32, 3.58)	0.697	-0.91 (-5.52, 3.70)	0.695

[a] Adjusted for caffeine intake during pregnancy, HOME at 6 month, maternal education, annual income and child sex for all subjects.

Table 6. Association between BSID-II (MDI, PDI) at 18 month and natural log transformed cord blood BPA concentration (N=86).

	Crude		Adjusted[a]	
All	β	p-value	β	p-value
MDI @ 18 month	-0.98 (-4.91, 2.96)	0.623	0.08 (-3.71, 3.87)	0.968
PDI @ 18 month	-0.93 (-4.96, 3.11)	0.648	0.69 (-3.34, 4.72)	0.735
Male	β	p-value	β	p-value
MDI @ 18 month	-0.91 (-7.40, 5.57)	0.777	-0.09 (-6.51, 6.34)	0.978
PDI @ 18 month	-2.79 (-9.00, 3.43)	0.369	-2.05 (-9.11, 5.01)	0.557
Female	β	p-value	β	p-value
MDI @ 18 month	-0.39 (-5.21, 4.43)	0.871	-0.96 (-5.88, 3.96)	0.695
PDI @ 18 month	0.75 (-4.40, 5.91)	0.770	2.28 (-3.10, 7.65)	0.398

[a] Adjusted for HOME at 18 month, maternal education, annual income and child sex for all subjects.

ビスフェノールAの胎児期曝露による免疫機能への影響
- 臍帯血IgEおよび乳幼児期のアレルギー症状，感染症との関連 -

研究分担者　佐々木 成子　北海道大学大学院医学研究科社会医学講座公衆衛生学分野助教
研究分担者　松村 徹　　いであ株式会社環境創造研究所副所長
研究代表者　岸 玲子　　北海道大学環境健康科学研究教育センター特任教授

研究要旨

ビスフェノールA（BPA）はポリカーボネートプラスチック製品やエポキシ樹脂製品に使用される化学物質で，ヒトへの曝露は主に経口的であるが，経皮的あるいは吸入によっても起こる。ヒト胎児期のBPA曝露による免疫機能への影響はまだ一致した結果が得られていないことから，臍帯血中BPA濃度を測定して，臍帯血IgEおよび乳幼児期のアレルギー症状，感染症との関連を検討した。臍帯血中IgE濃度との関連は認められなかったが，男児では，臍帯血中BPA濃度が約2.7倍になると，生後18ヵ月までの中耳炎のオッズ比が6.53（95% CI: 1.35, 31.57）と有意に上昇した。

研究協力者
山本 潤
（いであ株式会社環境創造研究所）

A．研究目的

ビスフェノールA（BPA）はポリカーボネートプラスチック製品やエポキシ樹脂製品に使用される化学物質である。ヒトへの曝露は主に経口的であるが，経皮的あるいは吸入によっても起こる。BPAは内分泌かく乱化学物質としてエストロゲン類似作用やアンドロゲン阻害作用により正常な細胞機能をかく乱することが示唆されている。

動物実験ではマウス仔で喘息発症と関連があり，また胎仔期のBPA曝露によりアレルギー感作，気道過反応，気管支好酸球増加性炎症が増強したと報告された。妊婦の母体尿中BPA濃度を胎児期曝露の指標としたヒト疫学研究では，BPA濃度が増加すると生後6ヵ月児の喘鳴リスクが上昇したという報告がある一方で，胎児期BPA曝露は5歳児の喘鳴リスクと負の関連を示し，生後のBPA曝露で幼児期の喘鳴リスクが上昇したとされるなど，まだ一致した結果は得られていない。

本研究では，微量試料中BPA高精度測定法を用いて臍帯血中のBPA濃度を測定し，胎児期BPA曝露による乳幼児期の免疫機能への影響を検討する。

B．研究方法

札幌市内一産院コーホートに登録した母児514名について，自記式質問票で母親と配偶者の妊娠中の喫煙・飲酒状況，食生活や教育歴，世帯収入などを調査し，医療診療録から産科既往歴や分娩時所見などに関する情報を入手した。児の18ヵ月時には，母親による自記式質問票で児の健康調査を実施し，18ヵ月時の体格，アレルギー症状および感染症の既往歴・現病歴，母乳栄養，集団保育歴，児の受動喫煙状況などについて390名から回答を得た。

臍帯血中のBPA濃度は，同位体希釈LC-MS/MS法（検出下限値0.048 ng/mL）で測定した。また，臍帯血血清中総IgE濃度は，ELISA法（検出下限値0.05 IU/mL）で（株）SRLにて測定した。

臍帯血中BPA濃度とIgE濃度との関連をみるために，両方の測定結果が揃った

152名を解析対象とした。BPA濃度とIgE濃度は自然対数変換し，検出下限値（LOD）以下の場合は半値を代入した。最終的に母の年齢，出産経歴，教育歴，妊娠中の喫煙状況，両親のアレルギー疾患既往歴および児の性別で調整した重回帰分析を行った。さらに，BPA濃度と児の18ヵ月までのアレルギー症状および感染症との関連をみるために，両方のデータが得られた136名についてロジスティック回帰分析を行った。アレルギー症状は母の教育歴，妊娠中の喫煙状況，両親のアレルギー疾患既往歴，児の性別，母乳栄養期間，18ヵ月時の家庭内受動喫煙および集団保育歴，感染症は母の教育歴，妊娠中の喫煙状況，児の性別，母乳栄養期間，18ヵ月時の家庭内受動喫煙および集団保育歴で調整した。

（倫理面への配慮）

北海道大学環境健康科学研究教育センターおよび北海道大学大学院医学研究科医の倫理委員会および研究協力施設の研究倫理委員会に諮り，承認を得たうえで実施した。

C．研究結果

解析対象者 152 名の母の平均年齢は，30.2±4.6歳，短大・大卒以上が56.6%（86名）初産婦は50.7%（77名），妊娠中に喫煙した者（途中禁煙者も含む）は35.5%（54名）であった。両親でアレルギー既往がある者は，母が30.9%（47名），父が16.4%（25名）であった。また，男児は45.4%（69名）であった。生後 18 ヵ月時の質問票に回答した136名では，家庭内で受動喫煙がある児が 46.3%（63名），集団保育されている児は18.4%（25名）であった（Table 1）。

臍帯血中BPA濃度は0.055 ng/mL（中央値），LOD（0.048 ng/mL）以下は40.1%（61 名）であった。臍帯血血清中 IgE 濃度は 0.22 IU/mL（中央値），LOD（0.05 IU/mL）以下は 15.1%（23 名）であった（Table 2）。児の出生から18ヵ月までのアレルギー症状および感染症の累積罹患率は，湿疹22.1%（30名），食物アレルギー20.6%（28名），喘鳴9.6%（13名），中耳炎18.4%（25名）で，男児では中耳炎の罹患が女児の約2倍であった（Table 3）。

臍帯血中BPA濃度とIgE濃度との関連を検討したが，交絡因子で調整しても有意な関連は認められなかった（Table 4）。また，臍帯血中BPA濃度と18ヵ月までの湿疹，食物アレルギー，喘鳴，中耳炎との関連についても調整前後で有意な関連は認められなかった。しかし，性別で層化したところ，男児では，臍帯血中 BPA 濃度が約2.7倍になると，中耳炎のオッズ比（OR）が調整なしで2.97（95% CI: 1.05, 8.38），調整後では6.53（95% CI: 1.35, 31.57）と有意に上昇した（Table 5）。

D．考察

母体尿中 BPA 濃度を曝露指標として胎児期 BPA 曝露による生後免疫機能の影響を検討したヒト疫学究では，妊娠 16 週の母体尿中BPA濃度が増加すると，6ヵ月児の喘鳴リスクが上昇したが，3 歳までにはその関連が減少し，妊娠 26 週や出生時のBPA曝露との関連はなかったことから，曝露の影響は妊娠初期の方が強いのではないかという報告がある。また，妊娠 16 週と26週のBPA曝露は4歳時の呼吸機能低下と関連があったが，生後の BPA 曝露については有意な関連は示さなかったという報告がある。一方，妊娠後期の胎児期曝露は5 歳児の喘鳴リスクと負の関連があり，生後のBPA曝露により5〜7歳の喘鳴リスクが上昇したという報告や，妊娠 12〜32 週のBPA曝露が生後6ヵ月〜7歳までの喘鳴や呼吸器感染症，気管支炎と関連があった

という報告など，これら先行研究では曝露評価時期やアウトカム評価時期が一様ではないため，結果の解釈が難しいと考えられる。また，健康アウトカムも喘鳴や喘息などの呼吸器疾患が主となっている。

動物実験では，マウスでBPA曝露によりアレルギー免疫反応が増大することが示唆されている。例えばハツカネズミでは，BPA曝露により制御性T細胞，IFN-γ，IL-10が減少し，IL-4産生と特異的IgE抗原が増加した。また，卵白アルブミン喘息モデルでは，ハツカネズミで胎児期BPA曝露が生後17日の抗卵白アルブミンIgE増加と気道の活動亢進に関与していた。さらに，マウスでは，胎児期と生後5週のBPA曝露によってアレルギー誘発Th2サイトカイン産生レベルが上昇したと報告されていることから，発達初期のBPA曝露は生後の免疫機能に影響があると考えられるが，そのメカニズムはまだ明らかではない。また，BPAは経口曝露後，ヒトでは代謝されたBPA-グルクロニドが肝臓から全身循環されて速やかに尿中に排泄されるのに対し，マウス，ラットなどのげっ歯類では胆汁中に排泄されて，腸管に存在するグルクロニダーゼによりBPAとグルクロン酸に解離されて再び血液中に吸収されるため，ヒトとげっ歯類では，BPAの体内動態に相違があり感受性が違うと考えられることから，BPA曝露によるヒトへの影響を解明するには，ヒトでのデータをさらに蓄積する必要がある。

本研究では，男児のみで胎児期 BPA 曝露により中耳炎 OR が上昇したが，同じコーホート集団で母体血中ダイオキシン類濃度と児の免疫機能を検討した報告では，2,3,4,7,8-PeCDF 濃度の第 1 四分位に対する第 4 四分位の中耳炎 OR が 2.8（95%CI: 1.2-6.6）と有意に上昇し，特に男児では，OR が 5.3（95%CI: 1.5-19.0）とさらに高くなったことから，化学物質への感受性は女児よりも男児で高い可能性が考えられる。アウトカム評価に関しては，生後 18 ヵ月までのアレルギー症状の確定診断が難しく，正確に結果に反映できなかったことも考えられるため，学童期までのアレルギー疾患・感染症の有病率との関連も評価していく予定である。

E．結論

臍帯血中の BPA 濃度を測定し，胎児期 BPA 曝露による乳幼児期の免疫機能への影響を検討した。臍帯血中 IgE 濃度との関連は認められなかったが，男児では，臍帯血中 BPA 濃度が約 2.7 倍になると，生後 18 ヵ月までの中耳炎 OR が 6.53（95% CI: 1.35, 31.57）と有意に上昇した。

先行研究では，成長に伴い免疫機能が変化することが報告されているので，今後は，学童期までの免疫機能への影響について検討していく。

F．研究発表

1）論文発表

なし

2）学会発表

なし

G．知的財産権の出願・登録状況

該当なし

参考文献

Donohue KM, Miller RL, Perzanowski MS, Just AC, Hoepner LA, Arunajadai S, et al. Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. J Allergy Clin Immunol. 2013;131:736-742.

Gascon M, Casas M, Morales E, Valvi D, Ballesteros-Gomez A, Luque N, et al. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol. In press.

Lee MH, Chung SW, Kang BY, Park J, Lee CH, Hwang SY, et al. Enhanced interleukin-4 production in CD41 T cells and elevated immunoglobulin E levels in antigen-primed mice by bisphenol A and nonylphenol, endocrine disruptors: involvement of nuclear factor-AT and Ca21. Immunology. 2003;109:76-86.

Midoro-Horiuti T, Tiwari R, Watson CS, Goldblum RM. Maternal bisphenol A exposure promotes the development of experimental asthma in mouse pups. Environ Health Perspect. 2010; 118:273–277.

Miyashita C, Sasaki S, Saijo Y, Washino N, Okada E, Kobayashi S, et al. Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy. Environmental Research. 2011;111:551-558.

Ohshima Y, Yamada A, Tokuriki S, Yasutomi M, Omata N, Mayumi M. Transmaternal exposure to bisphenol a modulates the development of oral tolerance. Pediatr Res. 2007;62:60-64.

Sawai C, Anderson K, Walser-Kuntz D. Effect of bisphenol A on murine immune function: modulation of interferon-gamma, IgG2a, and disease symptoms in NZB X NZW F1 mice. Environ Health Perspect. 2003; 111: 1883-1887.

Spanier AJ, Kahn RS, Kunselman AR, Hornung R, Xu Y, Calafat AM, et al. Prenatal exposure to bisphenol A and child wheeze from birth to 3 years of age. Environ Health Perspect. 2012; 120: 916-920.

Spanier AJ, Kahn RS, Kunselman AR, Schaefer EW, Hornung R, Xu Y, et al. Bisphenol A Exposure and the Development of Wheeze and Lung Function in Children Through Age 5 Years. JAMA Pediatr. 2014; 168(12): 1131-1137.

Strunk RC, Szefler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. J Allergy Clin Immunol. 2003; 112: 883-892.

Tian X, Takamoto M, Sugane K. Bisphenol A promotes IL-4 production by Th2 cells. Int Arch Allergy Immunol. 2003;132:240-247.

Yan H, Takamoto M, Sugane K. Exposure to Bisphenol A prenatally or in adulthood promotes T(H)2 cytokine production associated with reduction of CD4CD25 regulatory T cells. Environ Health Perspect. 2008;116:514-519.

Table1 Characteristics of subjects (n=152)

Characteristics	n (%)
Parental characteristics	
Maternal age (years)[a]	30.2 (4.6)
Maternal pre pregnancy BMI (kg/m^2)[a]	20.8 (3.0)
Parity	
0	77 (50.7)
≥1	75 (49.3)
Maternal education level (years)	
≤12	66 (43.4)
≥13	86 (56.6)
Maternal smoking status during pregnancy	
Nonsmoker	98 (64.5)
Smoker	54 (35.5)
Maternal allergic history	
No	105 (69.1)
Yes	47 (30.9)
Paternal allergic history	
No	127 (83.6)
Yes	25 (16.4)
Annual household income (million yen)	
<3	28 (18.4)
3-5	81 (53.3)
≥5	43 (28.3)
Distance from home to highway	
<100 m	72 (47.4)
≥100 m	80 (52.6)
Infant characteristics	
Gender	
Male	69 (45.4)
Female	83 (54.6)
Birth season	
Spring (March-May)	36 (23.7)
Summer (June-August)	44 (28.9)
Autumn (September-November)	34 (22.4)
Winter (December- Febuary)	38 (25.0)
Breast-feeding period (months) (n=134)	
<4	25 (18.7)
≥4	109 (81.3)
Environmental tobacco smoke exposure at 18 months (n=136)	
No	73 (53.7)
Yes	63 (46.3)
Day care attendance at 18 months (n=136)	
No	111 (81.6)
Yes	25 (18.4)

[a] Mean (SD)

Table2 Concentrations of BPA and concentrations of IgE in cord blood (n=152)

	Detection limit	ND[a], no. (%)	Mean	Minimum	25th	50th	75th	Maximum	Geometric Mean
Cord blood BPA (ng/mL)[b]	0.048	61 (40.1)	0.058	0.024	0.024	0.055	0.078	0.217	0.048
Cord serum IgE (IU/mL)[c]	0.05	23 (15.1)	0.66	0.03	0.09	0.22	0.55	10.90	0.23

[a] ND: not determined

[b] BPA: bisphenol A

[c] IgE: immunogloblin E

Table 3 Number of infants who developed allergies and infections during the firtst 18 months of life (n=136)

	Overall n (%)	Male n (%)	Female n (%)
Allergy			
Eczema	30 (22.1)	15 (23.1)	15 (21.1)
Food allergy	28 (20.6)	13 (20.0)	15 (21.1)
Wheezing	13 (9.6)	7 (10.8)	6 (8.5)
Infection			
Otitis media	25 (18.4)	16 (24.6)	9 (12.7)
Chicken pox	10 (7.4)	4 (6.2)	6 (8.5)
RSV disease[a]	3 (2.2)	0 (0)	3 (4.2)
Bronchitis	3 (2.2)	1 (1.5)	2 (2.8)
Pneumonia	2 (1.5)	0 (0)	2 (2.8)
Other viral infections[b]	6 (4.4)	4 (6.2)	2 (2.8)

[a] RSV disease: respiratory syncytial virus disease.

[b] Rotavirus, adenovirus or cytomegalovirus.

Table4 Association between BPA[a] concentrations (ng/mL) and IgE[b] concentrations (IU/mL) in cord blood (n=152)

	Crude		Adjusted[c]	
	β	95% CI	β	95% CI
log_eBPA				
Over all (n=152)	-0.019	(-0.385, 0.346)	-0.051	(-0.416, 0.314)
Male infants (n=69)	0.116	(-0.473, 0.704)	0.189	(-0.399, 0.776)
Female infants (n=83)	-0.146	(-0.614, 0.322)	-0.138	(-0.614, 0.339)

[a] BPA: bisphenol A

[b] IgE: immunogloblin E

c Adjusted models included maternal age, parity, maternal education level, maternal smoking status during pregnancy, parental allergic history, infant gender

Table5 Adjusted odds ratio (95% CI) between BPA concentrations in cord blood and allergies and infectious diseases during the first 18 months of life (n=136)

	Overall (n=152)				Male infants (n=69)				Female infants (n=83)			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
log_e BPA[b]												
Eczema[c]	1.14	(0.60, 2.20)	1.08	(0.54, 2.15)	1.39	(0.53, 3.64)	1.40	(0.47, 4.13)	0.96	(0.39, 2.36)	0.75	(0.25, 2.26)
Food allergy[c]	1.14	(0.58, 2.22)	1.21	(0.60, 2.46)	1.93	(0.68, 5.50)	3.05	(0.80, 11.6)	0.76	(0.30, 1.91)	0.62	(0.23, 1.71)
Wheezing[c]	1.16	(0.46, 2.90)	1.06	(0.40, 2.84)	1.20	(0.33, 4.42)	1.10	(0.24, 5.03)	1.10	(0.30, 4.07)	0.51	(0.09, 3.01)
Otitis media[d]	1.73	(0.85, 3.52)	1.78	(0.76, 4.10)	2.97	(1.05, 8.38)	6.53	(1.35, 31.57)	0.86	(0.28, 2.64)	0.82	(0.25, 2.65)

[a] OR for a 2.7-fold incrase in cord BPA concentrations

[b] BPA: bisphenol A

[c] Logistic regression model adjusted models for maternal education level, maternal smoking status during pregnancy, parental allergic history, infant gender, breast-feeding period, environmental tobacco exposure, day care attendance at 18 months.

[d] Logistic regression model adjusted models for maternal education level, maternal smoking status during pregnancy, infant gender, breast-feeding period, environmental tobacco exposure, day care attendance at 18 months.

Prenatal Exposure to Perfluorinated Chemicals and Neurodevelopment in Early Infancy

研究代表者 岸　玲子　　北海道大学環境健康科学研究教育センター 特任教授
研究分担者 池野 多美子　北海道大学環境健康科学研究教育センター 特任講師
研究分担者 宮下 ちひろ　北海道大学環境健康科学研究教育センター 特任講師
研究分担者 松浦 英幸　　北海道大学大学院農学研究院応用生命科学部門
生命有機化学分野生物有機化学研究室 准教授

研究要旨

We assessed the effects of perfluorooctane sulfonate (PFOS)/perfluorooctanoate (PFOA) concentrations, as most well detected PFCs in humans, on neurodevelopment of infants in early infancy. Mother-child pairs were analyzed in this birth cohort between 2002 and 2005 in Japan. The prenatal PFOS and PFOA levels were measured in maternal serum samples by liquid chromatography-tandem mass spectrometry. Neurodevelopment of infants at 6 and 18 months of age were assessed by Bayley Scales of Infant Development. Associations with log10-transformed PFC concentrations were estimated using linear regression models adjusted for potential confounders. In the fully adjusted model, PFOA, not PFOS, had a negative association with mental developmental index (MDI) among female infants. In addition, we observed negative association between PFOA and MDI/PDI at 18 months of age but it did not meet significant p-value. We observed no association between concentrations of PFOS and neurodevelopmental scores in infants. Our data suggest an inverse association between low-dose PFOA exposure and MDI in early life. In future studies, assessment of the effects of PFCs with longer carbon-chain on neurodevelopment of infants and children with bigger sample size and different battery tests is in need.

A. 研究目的

Perfluorinated chemicals (PFCs) are ubiquitous and stable chemicals widely detected in humans and environment. The most widely studied and detected PFCs are perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). They are slowly eliminated from the human body and are resistant to metabolism with mean half-lives of 5.4 and 3.8 years for PFOS and PFOA, respectively (Olsen et al. 2007). Both of these compounds showed neurodevelopmental toxicity in animal studies; maternal or neonatal exposure to PFOS and PFOA caused neurodelopmental delay, increased motor activity and reduced habituation that were accompanied by hypothyroxinemia (Lau et al. 2003; Butenhoff et al. 2009). A strong correlation of these compounds has been demonstrated between maternal and cord blood samples in

研究協力者
中島そのみ（札幌医科大学保健医療学部作業療法学科）
Houman Goudarzi
（北海道大学環境健康科学研究教育センター）
中澤 裕之、岩崎 雄介
（星薬科大学薬品分析化学教室）