Metabolic disruption in context: Clinical avenues for synergistic perturbations in energy homeostasis by endocrine disrupting chemicals

Robert M Sargis*
Committee on Molecular Metabolism and Nutrition; Kovler Diabetes Center; Section of Endocrinology, Diabetes, and Metabolism; Department of Medicine; University of Chicago; Chicago, IL USA

The global epidemic of metabolic disease is a clear and present danger to both individual and societal health. Understanding the myriad factors contributing to obesity and diabetes is essential for curbing their decades-long expansion. Emerging data implicate environmental endocrine disrupting chemicals (EDCs) in the pathogenesis of metabolic diseases such as obesity and diabetes. The phenylsulfamide fungicide and anti-fouling agent tolyfluanid (TF) was recently added to the list of EDCs promoting metabolic dysfunction. Dietary exposure to this novel metabolic disruptor promoted weight gain, increased adiposity, and glucose intolerance as well as systemic and cellular insulin resistance. Interestingly, the increase in body weight and adipose mass was not a consequence of increased food consumption; rather, it may have resulted from disruptions in diurnal patterns of energy intake, raising the possibility that EDCs may promote metabolic dysfunction through alterations in circadian rhythms. While these studies provide further evidence that EDCs may promote metabolic dysfunction through alterations in circadian rhythms. While these studies provide further evidence that EDCs may promote the development of obesity and diabetes, many questions remain regarding the clinical factors that modulate patient-specific consequences of EDC exposure, including the impact of genetics, diet, lifestyle, underlying disease, pharmacological treatments, and clinical states of fat redistribution. Currently, little is known regarding the impact of these factors on an individual’s susceptibility to environmentally-mediated metabolic disruption. Advances in these areas will be critical for translating EDC science into the clinic to enable physicians to stratify an individual’s risk of developing EDC-induced metabolic disease and to provide direction for treating exposed patients.

Introduction

Rates of diabetes mellitus are rising dramatically across the globe, threatening both individual health as well as the stability of national health systems. In the United States, diabetes is the leading cause of adult blindness, kidney failure, and non-traumatic amputations while also playing a central role in the development of cardiovascular disease, the leading killer of those with the disease. With estimates that diabetes currently affects nearly 24 million people in the US and that this number will rise to over 44 million individuals by 2034, the staggering $245 billion spent annually on diabetes-related healthcare costs is sure to rise dramatically. While these costs are unsustainable in the US where the healthcare infrastructure is robust and relatively well-funded, the burden of diabetes in the developing world may be catastrophic. Current projections estimate that 592 million individuals worldwide will have diabetes by 2035, with 77% of those individuals living in middle- or low-income countries with significantly less developed health systems. To prevent this threat from overwhelming health budgets across the globe, identification and elimination of the factors promoting the development of diabetes are essential.

The last decade has witnessed a proliferation of exciting epidemiological and basic science data suggesting that environmental contaminants play a pathogenic

Keywords: adipose, circadian rhythm, diabetes, EDCs, endocrine disruptor, glucose intolerance, insulin resistance, metabolic disease, obesity, tolyfluanid

© Robert M Sargis
*Correspondence to: Robert M Sargis; Email: rsargis@medicine.bsd.uchicago.edu
Submitted: 04/14/2015
Revised: 07/23/2015
Accepted: 07/30/2015
http://dx.doi.org/10.1080/23273747.2015.1080788
This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.
role in the development of metabolic disease (reviewed in refs. 5-7). Indeed, while initially implicated in perturbations of sex steroid and thyroid hormone signaling, environmental endocrine disrupting chemicals (EDCs) have now been shown to be associated with or to directly alter body weight and glucose homeostasis after either adult or developmental exposure (reviewed in refs. 5-7). Such metabolic disruptors include a diverse array of compounds such as bisphenol A, persistent organic pollutants (POPs), phthalates, antifouling agents, and pesticides. Our own recent work has added to this list a novel class of metabolism-perturbing agents, namely phenylsulfamide fungicides, as exemplified by tolyfluanid (TF). In this work, we’ve shown that dietary exposure to TF has the capacity to promote weight gain and increase adiposity despite not altering total food intake; rather, these changes appear to occur through altered circadian rhythms of food intake. Moreover, adult mice exposed to TF exhibited glucose intolerance as well as systemic and adipose-specific insulin resistance, phenotypic features commonly seen in the pathogenesis of type 2 diabetes. This new evidence provides further support to the contention that environmental change may play a critical role in the emergence of chronic diseases; however, many questions remain regarding the clinical scenarios in which EDCs exert their deleterious metabolic effects.

Under most circumstances, homeostatic mechanisms maintain normal energy metabolism and resist the development of cardiometabolic disease; however, several factors operating alone or in concert can lower this resistance to metabolic disease (RMD) and accelerate the progression of obesity, diabetes, hypertension, dyslipidemia, and cardiovascular disease (Fig. 1). While accidental or intentional ingestions of a single chemical may be sufficient to cause diabetes in select circumstances (e.g. the rodenticide Vacor9 and the fungicide chlorothalonil10), it is unlikely that a single chemical will be sufficient to explain the dramatic explosion in global diabetes rates. However, as there are tens of thousands of unique chemicals to which humans are potentially exposed, coordinate exposure to multiple EDCs that additively antagonize critical pathways regulating energy metabolism through complimentary mechanisms may be sufficient to promote cardiometabolic dysfunction, whereas a single signaling disruptor in isolation may be insufficient to drive significant disease.11 These EDC × EDC interactions may be critical for generating metabolic phenotypes from the chronic, low-dose exposures that characterize human contact with environmental toxins. Unfortunately, the experimental complexities of analyzing mixtures of metabolic disruptors are immense; however, some recent data demonstrate that such mixtures, at environmentally relevant doses, can disrupt energy handling,12,13 suggesting that further studies into common co-exposures are warranted. Alternatively, the potency of a metabolic disruptor might be enhanced by permissive conditions in specific patients that may predispose those individuals to environmentally-mediated metabolic disease. Such factors may include underlying genetics, diet, lifestyle, preexisting diseases, pharmacological treatments, and states of fat redistribution that alter the patient’s baseline physiology in such a way as to increase their sensitivity to metabolic disruption.

**Genetic Sensitivity to Metabolic Disruption**

Our recent work demonstrates that dietary exposure to TF increases adiposity, promotes glucose intolerance, and decreases insulin sensitivity both globally and at the level of the adipocyte.8 Like many metabolic investigations, these studies employed the C57BL/6 strain. While we had previously shown that ex vivo exposure to TF induced adipocytic insulin resistance in outbred CD1 mice, inbred C57BL/6 mice, 2 strains of rats, and even human adipose tissue,14 whether the observed effects on global energy homeostasis are influenced (either positively or negatively) by the background genetics of the animal model is not known. In the
The Impact of Diet on EDC-Induced Metabolic Disruption

It is clear that the deteriorating quality of our diet plays an important role in promoting the development of obesity and diabetes; moreover, the exportation of the American diet may be a significant contributor to the global plague of metabolic disease. 

Despite the importance of diet in modulating energy handling, the impact of these global shifts in diet composition on EDC action has only recently been interrogated. To date, the interactions between EDCs and dietary stressors in the disruption of energy homeostasis has largely been interrogated in the context of high fat feeding. Indeed, potentiation of metabolic disruption by a high fat diet has been demonstrated for bisphenol A, perfluorooctane sulfonate, POPs, and chemical mixtures. Interestingly, our metabolic cage analyses suggest that mice exposed to TF have a preference for fat over carbohydrate utilization during the fed state. This suggests that diets rich in carbohydrates, or the simple sugars enriched in a "Western Diet," may be particularly deleterious in the context of exposure to TF and potentially other EDCs. This may be significant as the transformation of the American diet over the last 30 years has been one of increased carbohydrate content, particularly the refined grains and simple sugars found in processed foods. As increased fructose intake has been implicated in the explosion in diabetes rates, understanding how EDCs interact with secular trends in dietary carbohydrate content and composition will be important for contextualizing the importance of EDCs in the current metabolic disease epidemic. Furthermore, as the burden of diabetes spreads to low- and middle-income countries, understanding how EDCs interact with specific dietary factors in these countries will be essential for estimating the risk posed by environmental toxicants as drivers of the metabolic disease epidemic in the developing world.

Lifestyle and the Susceptibility to Metabolic Disruption

An intriguing finding of our work on TF was that adiposity (fat mass as a fraction of total body mass) and weight gain were increased in the presence of this EDC despite no change in total food intake. We were, however, able to discern an intriguing change in the circadian pattern of food intake, with TF-exposed mice consuming more food during the normally fasting light-phase. This evidence provides some of the first experimental support for EDC-induced disruptions in energy homeostasis arising through perturbations in circadian rhythms. In humans, experimental disruptions in circadian rhythms are associated with deleterious changes in energy handling. 

Clinically, the timing of food intake has been shown to contribute to weight gain. Moreover, individuals who consume more calories at night may have a harder time losing weight. This raises several intriguing questions. First, does EDC exposure itself increase food consumption during normal fasting periods? Second, do EDCs augment the deleterious metabolic effects of disruptions in circadian patterns of food intake that are driven by lifestyle factors that are intentional (e.g., night eating) or forced (e.g., shift work)? And finally, if alterations in circadian rhythms are wholly or partially responsible for EDC-induced obesity and
diabetes, will restriction of food intake to
the normal feeding period be an appropri-
ate treatment approach? Studies examin-
ing the lifestyle factors that exacerbate or
antagonize the deleterious effects of EDCs
on energy homeostasis may provide vital
insights into both the mechanisms of
EDC-induced metabolic dysfunction as
well as potential avenues to treat toxicant-
mediated metabolic disease. Beyond influ-
ences of feeding behavior, understanding
how EDCs modulate central processes
such as motivation may help explain diffi-
culties patients have self-regulating food
intake and sustaining exercise, as will stud-
ies of EDC effects on skeletal muscle,
which remains an understudied area of
metabolic toxicity.

Disease-Induced Sensitivity to
EDC-Mediated Metabolic
Perturbations

Some of the early evidence suggesting
EDCs have the capacity to alter energy
metabolism came from studies examining
their ability to promote adipocyte differen-
tiation from preadipocytes or mesen-
chymal stem cells. In many of these
studies the 3T3-L1 cell line is used as a
model of adipogenesis, with preadipocyte-
to-adipocyte differentiation classically
induced by exposure to insulin, a gluco-
corticoid, and an agent to raise cAMP lev-
elks. The capacity of various EDCs to
amplify adipose development can be stud-
ied by triggering adipogenesis with this
differentiation cocktail in the presence or
absence of the EDC of interest. By this
approach, many environmental contami-
nants have been shown to promote adipo-
cyte differentiation (reviewed in ref.42).
As we have recently dissected for the proto-
typical obesogen tributyltin, most EDCs
appear to require one or more compo-
nents of the differentiation cocktail to
induce adipogenesis. As such, it is possible
that clinical states that modulate those
specific pathways could augment the adi-
pogenic capacity of EDCs. For example,
hyperinsulinemic states, as observed in
prediabetes or early type 2 diabetes, may
sensitize mesenchymal stem cells and prea-
dipocytes to EDC-induced adipocyte dif-
ferentiation for chemicals requiring co-
exposure to insulin to induce adipogene-
sis. Similarly, clinical states of high adren-
ergic tone that are predicted to raise
intracellular cAMP levels may potentiate
the action of some adipogenic EDCs that
require pre-activation of cAMP signaling.
One example of this is obstructive sleep
apnea (OSA), a common disease linked to
metabolic dysfunction. Likewise, EDCs
that require glucocorticoids to promote
adipocyte development may exhibit
enhanced adipogenic capacity in individu-
als with hyperactivation of the hypothal-
amic-pituitary-adrenal (HPA) axis who
exhibit high glucocorticoid levels or
enhanced glucocorticoid receptor (GR)
signaling. Such clinical states include
Cushing’s syndrome, pseudo-Cushing’s
syndrome, OSA, or even endogenous obe-
sity. We demonstrated that TF activ-
ates adipocytic GR signaling both ex vivo
and in vivo, suggesting one mechanism
by which this novel endocrine disruptor
promotes metabolic dysfunction. It
remains to be determined whether clinical
states of heightened GR signaling potenti-
ate TF action. It is interesting, however,
to speculate that other EDCs that inhibit
the enzymes responsible for glucocorticoid
inactivation, 11β-hydroxysteroid dehy-
drogenases, might exhibit enhanced
metabolism-disrupting potency in clinical
states of glucocorticoid excess (e.g., dithio-
carbamates and organotins). Whether
an individual’s underlying disease state
renders them more susceptible to EDC-
mediated metabolic disruption has not
been studied, but knowledge of the mecha-
nisms by which these environmental toxi-
cants disrupt nutrient handling and the
development of metabolic tissues may sug-
gest that, under certain clinical scenarios,
some individuals may be primed for
environmentally-mediated alterations in
energy metabolism.

Pharmaceutical-Enhanced
Susceptibility to Metabolic
Disruptors

Reciprocal to the concept that underly-
ing diseases might augment an individu-
al’s sensitivity to the deleterious metabolic
effects of an EDC, disease treatments
themselves may generate a permisive
environment under which EDCs induce
metabolic dysfunction. As argued for
states of endogenous corticosteroid over-
production, pharmacological treatment
with glucocorticoids, as employed in the
care of individuals with inflammatory dis-
ases, may potentiate the action of EDCs
working through or in conjunction with
GR signaling. Similarly, treatment with
adrenergic agonists that raise cAMP levels
may prime preadipocytes for differentia-
tion upon exposure to some EDCs. For
example, standard treatment approaches
to asthma, a highly prevalent lung disease,
with β2-adrenergic agonists such as albu-
terol, may generate a permissive environ-
ment for EDC-induced adipogenesis. As
our knowledge of the mechanisms by
which EDCs exert deleterious metabolic
effects expands, we will be better equipped
to predict how various disease states and
their treatments may render a subset of
patients particularly sensitive to environ-
mental contaminants modulating those
pathways. Conversely, knowledge of the
mechanisms by which EDCs induce meta-
bolic disease may suggest therapeutic ave-
nues to treat environmentally-mediated
obesity and diabetes or identify individu-
als whose exposure to certain EDCs
should be aggressively limited. Finally,
future studies may take advantage of the
known mechanisms by which anti-dia-
abetic medications lower blood sugar (e.g.,
sulfonylurea receptor, peroxisome prolifer-
ator-activated receptor-γ, AMP-acti-
vated protein kinase, sodium-glucose
co-transporter-2, incretin receptors, etc.) to:

a) unravel the molecular mechanisms of
    metabolic disruption; b) identify
    potential EDC-drug antagonism that
    limit therapeutic efficacy; and c) develop
    molecularly-based approaches to treat
    EDC-mediated diabetes in a new era of
    precision environmental medicine.

Clinical States of EDC
Repartitioning and Metabolic
Dysfunction

A core therapy for myriad metabolic
diseases is weight loss. Whether achieved
through dietary interventions, exercise,
anti-obesity drugs, or surgery, reductions
in body weight have multiple salutary
effects on energy metabolism and overall health, effectively raising R_{MD} in the disease progression model (Fig. 1). However, because adipose tissue serves as a reservoir for lipophilic EDCs, mobilization of fat with weight loss is accompanied by a repartitioning of these chemicals from adipose tissue into the circulating plasma compartment. This has been shown in several human studies examining caloric restriction with or without a weight loss drug. A similar study also showed an inverse association between the extent of weight loss and insulin levels. It is interesting to speculate that this reduction in insulin levels could be compensation for EDC-induced impairments in hepatic gluconeogenesis as we have shown for dioxin-like PCBs. Importantly, reductions in total fat mass have also been shown to concentrate pollutant levels in adipose tissue, suggesting that adipocyte physiology may also be deleteriously affected by effective increases in EDC concentrations in this important metabolic tissue induced through weight loss. Whether this repartitioning of putative metabolic disruptors partially antagonizes further weight loss or its metabolic benefits requires further investigation, as does the hypothesis that adipose expansion itself protects against EDC-induced metabolic dysfunction through fat sequestration that limits EDC action on non-adipose tissues. Finally, the impact of clinical states of altered adipose development, e.g., congenital and acquired lipodystrophies, on an individual’s sensitivity to environmental contaminants necessitates interrogation as individuals with these diseases may be especially vulnerable to EDC-induced metabolic dysfunction due to a reduced capacity to safely sequester lipophilic pollutants.

An analogous clinical state of EDC repartitioning that results from energy shifts and promotes systemic pollutant release is lactation. Many studies from diverse geographical regions have demonstrated the presence of various environmental contaminants in breast milk, including POPs such as PCBs and organochlorine pesticides. Importantly, while EDC elimination through lactation may be an important mode by which the total body burden of pollutants is reduced in the mother, the subsequent exposure of the developing newborn to these EDCs during this critical developmental period may be especially deleterious for the long-term metabolic health of the child as suggested by the DOHaD hypothesis. Interestingly, while the metabolism-disrupting potency of EDCs to which an individual is exposed in adulthood is likely enhanced by that individual’s clinical status (e.g., lifestyle factors, underlying diseases, and medications), it is also possible that early life EDC exposures potentiate the adverse metabolic consequences of those same clinical factors later in life. Improved understanding of the impact of exposure to EDCs through breast milk on later life energy homeostasis is of critical importance for both predicting risk and developing novel treatment strategies to address pollutant-induced metabolic dysfunction.

Conclusions

Our recent work demonstrating that dietary exposure to the phenylsulfamide fungicide TF promotes weight gain, adipose accretion, and glucose intolerance as well as systemic and cellular insulin resistance provides further support to the theory that environmental toxicants likely contribute to the current global epidemic of metabolic disease. While exposure to certain EDCs has been shown to be sufficient to initiate the development of diabetes, this occurs rarely. It is more likely that the contribution of EDCs to the current epidemic of obesity and diabetes results from coordinate exposures to multiple EDCs, each affecting the same or complementary signaling pathways that regulate energy handling. Alternatively, EDC-mediated metabolic dysfunction may be enhanced or accelerated by patient-specific parameters that alter an individual’s sensitivity to metabolic disruption, including underlying genetics, diet, lifestyle factors, preexisting diseases, pharmaceuticals, and clinical states of fat redistribution. More comprehensive understanding of the complex interplay between these patient-specific variables and EDC action will be essential for determining the contribution of environmental pollutants to the current epidemic of metabolic disease and for devising strategies to address the threat of environmental degradation on human metabolic health.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Funding
This work was supported by a Pilot and Feasibility Grant from the NIH-funded University of Chicago Diabetes Research and Training Center (P60-DK020595), a Junior Investigator Award from the Brinson Foundation, an Early Career Development Award from the Central Society for Clinical and Translational Research, and the National Institutes of Health (K08-ES019176 and R21-ES021354).

References

1. American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care 2015; 38(Suppl): S4; PMID:25537706; http://dx.doi.org/10.2337/diabetes caredx.doi.org/10.2337/db11-0153
2. Huang ES, Bau A, O’Grady M, Capretta JC. Projecting the future diabetes population size and related costs for the U.S. Diabetes care. 2009; 32:2225-9; PMID:19940225; http://dx.doi.org/10.2337/dc09-0459
3. ADA. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013; 36:1033-46; PMID:23468086; http://dx.doi.org/10.2337/dc12-2625
4. IDF. Diabetes atlas. Brussels, Belgium: International Diabetes Federation; 2013.
5. Kao CC, Moon K, Thayer KA, Navas-Acien A. Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. Curr Diab Rep 2013; 13:831-49; PMID:24114039; http://dx.doi.org/10.1007/s11892-013-0452-6
6. Thayer KA, Heinidel JJ, Buchter JR, Gullo MA. Role of environmental chemicals in diabetes and obesity: a national toxicology program workshop review. Environ Health Perspect 2012; 120:779-89; PMID:22296744; http://dx.doi.org/10.1289/ehp.1104597
7. Neel BA, Sarge RM. The paradox of progress: environmental disruption of metabolism and the diabetes epidemic. Diabetes 2011; 60:1838-48; PMID:21709279; http://dx.doi.org/10.2337/db11-0153
8. Regnier SM, Kirkley AG, Ye H, El-Haddany E, Zhang X, Neel BA, Kamau W, Thomas CC, Williams AK, Hayes ET, et al. Dietary exposure to the endocrine disruptor tolyfluanid promotes global metabolic dysfunction in male mice. Endocrinology 2015; 156:896-910;
21. Billings LK, Florez JC. The genetics of type 2 diabetes: what have we learned from GWAS? Ann N Y Acad Sci 2010; 1212:59-77; PMID:21091714; http://dx.doi.org/10.1111/j.1749-6632.2010.05838.x

22. Greetley SR, Naylor RN, Philipson LH, Bell GI. Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment. Curr Diab Rep 2013; 13:1159-32; PMID:23519633; http://dx.doi.org/10.1007/s11892-011-0254-7

23. Rubio-Cabero A, Hattersley AT, Njoland PR, Miy-narski W, Ellard S, White N, Chi DY, Craig ME. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2014; 15 (Suppl 20): 215-32; PMID:25182907; http://dx.doi.org/10.1111/pedi.12192

24. Consortium STT, Estrada K, Aukrust P, Bjorbaek C, Burtt NP, Mercader JM, Garcia-Ortiz H, Huerta-Chagoya A, Moreno-Macias H, Walford G, et al. Association of low-frequency variants in HSF1A with type 2 diabetes in a Latino population. JAMA 2014; 313:2390-4; PMID:24915262; http://dx.doi.org/10.1001/jama.2014.6511

25. Naylor RN, John PM, Winn AN, Carnady D, Greetley SA, Philipson LH, Bell GI, Huang ES. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. Diabetes care 2014; 37:202-9; PMID:24026547; http://dx.doi.org/10.2337/dc13-0880

26. Poplin RM, Gordon-Larsen P. The nutrition transition: worldwide obesity dynamics and their determinants. Int J Obes Relat Metab Disord 2004; 28(Suppl 3):s2-9; PMID:15544214; http://dx.doi.org/10.1038/oby.2004.158

27. Ahima RS. Digging deeper into obesity. J Clin Invest 2011; 121:2067-79; PMID:21633174; http://dx.doi.org/10.1172/JCI45781

28. Ding S, Fan Y, Zhao N, Yang H, Ye X, He D, Jin X, Liu J. Tissue-specific and the epidemic of T2D: a study of diabetes in the Yangdi population. Acta Diabetol 2017; 54:177-86; PMID:28243214; http://dx.doi.org/10.1007/s00592-016-1001-x

29. Wei J, Lin Y, Li, Ying C, Chen J, Song L, Zhou Z, Ly Z, Xia W, Chen X, et al. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. Endocrinology 2011; 152:3049-61; PMID:21586551; http://dx.doi.org/10.1210/me.2012-1270

30. Han HT, Zhao YG, Leung PY, Wong CK. Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult mice. PloS one 2014; 9:e87137; PMID:25108435; http://dx.doi.org/10.1371/journal.pone.0087137

31. Ibrahim MM, Fjaere E, Lock NJ, Naville D, Amlund H, Meugnier E, Le Magueresse Battistoni B, Froyland C, Begeot M, et al. Low-dose food contaminants trigger development of a phenotypically distinct adipocyte. Obesity 2015; PMID:26243053; http://dx.doi.org/10.1002/oby.21714

32. Somers VK, Dyken ME, Clay PR, Ababbous FM. Sym- pathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; 96:1897-904; PMID:7560081; http://dx.doi.org/10.1172/JCI118235

33. Woods C, Corrigan M, Gathercole I, Taylor A, Hughes R, Gaoxue G, Manalopulos K, Hogan A, Connell J, Stewart P, et al. Pericardial fat accumulation of glucocorticoids in severe obesity and the response to significant weight loss following bariatric surgery (BAR-ICORT). J Clin Endocrinol Metab 2015; 100 (4):1439-44; e1414;doi:10.1210/jc.2015-3693; PMID:26504361

34. Koo HY, Wallig MA, Chung BH, Nara TY, Cho BH, Manolopoulos K, Hungerford T, et al. Bile acid and human adipocytes through a reduction in insulin sensitivity and obesity in mice. PloS One 2013; 8:e62491; PMID:24026547; http://dx.doi.org/10.1371/journal.pone.0062491

35. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Timing of food intake as a potential therapeutic target for obesity and related metabolic disorders. Chronobiol Int 2013; 30:1249-73; PMID:23681665; http://dx.doi.org/10.3945/an.112.002998

36. Woods C, Corrigan M, Gathercole I, Taylor A, Hughes R, Gaoxue G, Manalopulos K, Hogan A, Connell J, Stewart P, et al. Pericardial fat accumulation of glucocorticoids in severe obesity and the response to significant weight loss following bariatric surgery (BAR-ICORT). J Clin Endocrinol Metab 2015; 100 (4):1439-44; e1414;doi:10.1210/jc.2015-3693; PMID:26504361

37. Greenbaum JC, Mlera R, Mathur S, Amlou V, Ashraf M, et al. Use of food in the diagnosis and differential diagnosis of Cushing’s syndrome: a consensus statement. J Clin Endocrinol Metab 2007; 92:5593-602; PMID:17461138; http://dx.doi.org/10.1210/jc.2007-038071

38. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing’s syndrome and pseudo-Cushing’s states. Endor Rev 1998; 19:647-72; PMID:9793762

39. Neel BA, Brady MJ, Sargis RM. The endocrine disrupting chemical tof fluorinated alcohols adipocyte metabolism via glucocorticoid receptor activation. Mol Endocrinol 2013; 27:394-406; PMID:23540252; http://dx.doi.org/10.1210/me.2012-1270

40. Atanasov AG, Tam S, Rickem JM, Baker ME, Oder- mant A. Inhibition of 11β-hydroxysteroid dehydroge- nase type 2 by dichlorobenzenes. Biochem Biophys Res Commun 2005; 328:257-62; PMID:12901862; http://dx.doi.org/10.1016/j.bbrc.2005.03.015

41. Atanasov AG, Nashew LG, Tam S, Baker ME, Oder- mant A. Orangotins disrupt the 11β-hydroxysteroid dehydrogenase type 2–dependent local inactivation of glucocorticoids. Environ Health Perspect 2005; 113:1600-6; PMID:16262518; http://dx.doi.org/10.1289/ehp.8209

42. Onderman A, Gunmy C, Atanasov AG, Dyakkhanchuk AA. Disruption of glucocorticoid action by environ- mental chemicals: potential mechanisms and relevance. J Steroid Biochem Mol Biol 2006; 102:222-31; PMID:17045799; http://dx.doi.org/10.1016/j.jsbmb.2006.09.010

43. Chevre J, Dewaull J, Eayote P, Maurie P, Desprets JP, Tremblay A. Body weight loss increases plasma and
adipose tissue concentrations of potentially toxic pollutants in obese individuals. Int J Obes Relat Metab Disorders 2000; 24:1272-8; PMID:11093288; http://dx.doi.org/10.1038/sj.ijo.0801380

53. Hue O, Marcotte J, Berrigan F, Simoneau M, Dore J, Marceau P, Marceau S, Tremblay A, Teasdale N. Increased plasma levels of toxic pollutants accompanying weight loss induced by hypocaloric diet or by bariatric surgery. Obes Surg 2006; 16:1145-54; PMID:16985079; http://dx.doi.org/10.1381/096089206778392356

54. Imbeault P, Desaive C, Plomteux G. Human exposure to endocrine disrupters: consequences of gastroplasty on plasma concentration of toxic pollutants. Int J Obes Relat Metab Disorders 2002; 26:1465-8; PMID:12439648; http://dx.doi.org/10.1038/sj.ijo.0802144

55. Wang H, Suri RP, Bi X, Sheng S, Fu J. Exposure of young mothers and newborns to organochlorine pesticides (OCPs) in Guangzhou, China. Sci Total Environ 2010; 408:3133-8; PMID:20471063; http://dx.doi.org/10.1016/j.scitotenv.2010.04.023

56. Shen H, Maitin RM, Anderson AM, Dungaard IN, Virtanen HE, Skakkebæk NE, Toppari J, Schramm KW. Concentrations of persistent organochlorine compounds in human milk and placenta are higher in Denmark than in Finland. Hum Reprod 2008; 23:201-10; PMID:18025027; http://dx.doi.org/10.1093/humrep/den199