Diabetes

Could low-level background exposure to persistent organic pollutants contribute to the social burden of type 2 diabetes?

Duk-Hee Lee, David R Jacobs Jr, Miquel Porta

Persistent organic pollutants may contribute to cause diabetes

Persistent organic pollutants (POPs) include hundreds of different chemical compounds with common properties, such as long-term persistence, widespread diffusion in the environment and bioaccumulation through the food chain.[1–3] In various species, POPs are linked to cancer, neurobehavioural disorders, impaired immunity, endocrine problems and reproductive disorders. Most epidemiological findings to date have focused on people with high exposure to POPs in occupational or accidental settings, whereas people without such high exposure have been much less studied; with few exceptions, this approach has uncovered only modest associations with various health outcomes.[2 4]

POPs are detectable in virtually all of the general population, most of whom experience only background exposure through food consumption[1–3]; a substantial body of biological, clinical and epidemiological knowledge suggests that such chronic low-level exposure is unlikely to be risk-free. An example useful for the discussion on this issue is provided by a recent study conducted by our research groups in Korea and Minnesota, based on a random sample of the US general population—that is, a sample with only background exposure to POPs.[5] The study found a rather striking positive dose–response relationship between prevalence of type 2 diabetes and serum concentrations of several individual POPs, as well as with a summary or composite of the serum concentrations of six of the POPs with highest concentrations. After adjusting for known risk factors for diabetes, and compared with people with non-detectable POPs, the prevalence of type 2 diabetes increased by 15–40-fold among those with detectable concentrations of POPs.[5] Undoubtedly, we should be cautious about this finding: it is cross-sectional and has not been replicated, although it is in line with several previous findings.

Remarkably, no prospective study on the potential relationship between body burden of POPs and incident diabetes has been carried out in the general population; such studies are urgent. If all the excess risks observed[5] were causal, the effect on public health could be huge. This hypothesis is made with the full understanding that obesity is the primary risk factor for type 2 diabetes. The study included 463 people in the lowest quartile of the composite of the six POPs[5]; of them, 34% were overweight and 28% were obese, yet only one overweight and one obese person had prevalent diabetes. Both the 0.4% prevalence in the whole group of 463 and the 0.7% prevalence in the 287 overweight and obese people are much lower than the 10.8% prevalence in the total 2016 men and women studied. Hence, the hypothesis (again, unreplicated) is that obesity might be only weakly associated with diabetes among people with very low serum concentrations of POPs, suggesting that the POPs stored in the adipose tissue may be a key in the pathogenesis of type 2 diabetes rather than obesity itself. If this speculation eventually proved to be true, the current paradigm on the mechanisms involved in the relationship between obesity and type 2 diabetes would need to be reconsidered.

At first, this line of thought may seem to be contradicted by the observation that the average body burden of several POPs has declined in several industrialised countries over recent decades,[6] a time when the occurrence of type 2 diabetes has increased in many parts of the world. However, the study observed a possible interaction between POPs and obesity on the risk of type 2 diabetes: patients in the top decile of the composite of the six POPs had ''only'' a 16-fold excess risk of diabetes if they were of normal weight, whereas the risk of diabetes was 50-fold among the obese.[5] Thus, the recent epidemic of obesity may explain the finding; as people get fatter, the retention and toxicity of POPs related to the risk of diabetes may increase. In addition, other POPs such as the brominated flame retardants, perfluorinated compounds or chlorinated paraffins, which are still in widespread use today,[7] may be as important as the POPs that were measured in the National Health and Nutrition Examination Survey. In fact, proper studies—including time-series and age-period-cohort analyses—on the relationships among POP concentrations in the general population, obesity and diabetes are surprisingly lacking. In the past few decades, exposures are likely to have varied widely for different POPs; for example, for pesticides such as dichloro diphenyl trichloroethane and for industrial products such as polychlorinated biphenyls (PCBs), which had very different time and commercial origins, dynamics of use and regulations throughout the planet. The periods, geographical areas and populations that they contaminated are likely to have been very different. The available evidence also suggests that human concentrations of some POPs—such as PCBs, lindane and the other hexachlorocyclohexanes and hexachlorobenzene—may not have continued to decline in all countries as steeply as they did initially. Jointly, all of these dynamic differences are likely to have had subtle, sometimes profound, often diverse effects on the risk of diabetes and other diseases. Hence, we need in-depth analyses of the relationships between low-level contamination by POPs of the general population and obesity, diabetes and other health effects. Two components of such studies should be that diabetes and POPs are measured in human fluids and that the studies are based on samples of the general population. These are precisely two unique strengths of the study we here use to focus on the discussion.[5]

Although the findings[5] have biological plausibility from experimental and clinical studies,[8–11] it is essential to keep in mind that they are cross-sectional. Reverse causality is possible: metabolic changes caused by diabetes might influence the distribution and elimination of lipophilic compounds such as POPs.[12] However, the toxicokinetic evidence in diabetes is weak. Also, if this scenario were real, much stronger associations between POPs and diabetes should have been observed in previous studies than were observed, because POP exposure levels were much higher in those studies[13 14] than in our sample.[5] Furthermore, the weak association between obesity and diabetes in the lowest quartile of the composite of the six POPs cannot be explained by the cross-sectional nature of the study.

How could the strength of association in the study[5] be so much stronger than

in previous studies, despite the much higher serum concentrations of POPs that occur after exposure to POPs in occupational or accidental settings? We suggest that epidemiological design considerations played an important part. Selection of the reference group may have been a key point. In our study, the risk of diabetes started to rise severely from the second quartile of the composite of the concentrations of the six POPs with highest concentrations (adjusted odds ratio of about 15 for that second quartile). With such a steep risk gradient, pooling across apparently low levels of serum POPs could result in falsely low relative risk levels for those with higher exposure to POPs. Most previous epidemiological studies have compared people with exposure to high concentrations of POPs in an occupational or accidental setting to the general population with only background exposure. If our study is correct and a steep risk gradient exists across background exposure levels, the approach used in the previous epidemiological studies may have substantially underestimated the strength of association of POPs with disease outcomes.

The second key point concerns the shape of the risk function. Despite the strong risk gradient across serum levels typical of background exposure, a correct relative risk estimate would still be obtained if there were a linear increase in diabetes risk across the full range of POP accumulation in serum in response to background high-level accidental exposure. Then, the selection of the reference group would not be so critical. Although ''routine thinking'' tends to dismiss findings as chance if associations are not monotonic, in health and life sciences there often is no linear dose–response relationship. POPs (or any other exposure) need not show a linear dose–response relationship with diabetes (or other health outcomes) for it to be true and meaningful. Although the strength of association in our study tended to increase as the concentrations of POPs increased, the association was much steeper across lower background concentrations than across higher background concentrations. This reduced acceleration of risk at higher levels of exposure to POPs is in agreement with toxicological findings. Increasing toxicity with increasing doses of 2,3,7,8-tetrachlorodibenzopara-dioxin or some polychlorinated biphenyls was even followed by a plateau or a decrease in toxicity at their higher doses.[15 16]

The third key epidemiological design point has to do with combining risk from several risk contributors. We evaluated a summary and synergic effect of multiple POPs that are commonly detected in the general population.[1–3] Previous epidemiological studies, however, focused mostly on exposure to only one or two POPs in occupational or accidental settings. By contrast, background exposure certainly includes a wide variety of POPs. As background exposure to POPs in the general population is a real problem, epidemiological studies need to analyse the joint effects of various kinds of POPs and allow for the possibility of additive or synergistic effects of many POPs, as well as for specific effects of particular POPs.

The association between POPs and diabetes detected by our approach is unusually strong. It reflects real conditions of exposure in most of the general population. However, the approach has the limitation that it will not necessarily identify which POPs are the actual causal agents in health, because the focus is primarily on those POPs that are easier to detect. Serum concentrations of various POPs are often correlated, including those that may be the true causal agents but exist at very low levels in serum.

Both type 1 and type 2 diabetes have β cell insufficiency, to a greater or lesser extent, as part of the pathogenesis.[17 18] The β cell toxin streptozotocin, typically used to induce type 1 diabetes in animals, can cause type 2 diabetes under certain conditions.[19] We raise the possibility that exposure to relatively high levels of POPs during pancreatic development in utero or in early infancy may lead to the development of type 1 diabetes among children, although the life-time exposure to low levels of POPs combined with obesity may be related to type 2 diabetes among adults. Even though twin studies have shown that both type 1 and type 2 diabetes have a genetic basis, the effects of most known diabetes-predisposing genes are weak.[17 18] Common exposure to POPs in utero could be an important linking factor. The causal role of POPs in diabetes is likely to be contributory and indirect (eg, through immunological, non-genotoxic and epigenetic mechanisms). On biological and clinical grounds, easy to measure ''main effects'' are implausible. A proper understanding of how genes and POPs interact to cause diabetes is important both for primary prevention and to further basic knowledge (on diabetogenic mechanisms, on genetic toxicology and on mechanisms of POP effects).

Additional issues need to be tackled on the possible association of POPs with type 2 diabetes and other adverse health outcomes. The concept of toxic equivalency factors, which is strongly linked to the ability of a chemical to bind to the aryl hydrocarbon receptor (AhR), was developed to facilitate risk assessment and regulatory control of exposure to complex POP mixtures.[20] Thus, studies sometimes use toxic equivalency factors to investigate the summary effect of POPs. However, many findings suggest that binding to the AhR is not the only mechanism and may not be the critical pathway.[3] For example, PCB congeners have differential effects on end points of neurotoxicity depending on their chemical structure: specifically, the ortho-substituted congeners that have a low affinity for the AhR are neurotoxic, whereas coplanar (dioxin-like) congeners that have a high affinity for the AhR are relatively inactive in producing neurotoxic effects.[21] In addition, as the background exposure to POPs comes from food consumption,[1 2] especially animal fat-containing food such as meat, fish and dairy products, dietary factors in POP-containing food may interact with POPs. Epidemiological studies on diet often completely overlook the fact that most of the fat-containing foods have low doses of POPs.[1] Pollutants in foods, such as POPs, could be as critical to risk as native constituents in food.

We need to understand the burden of diabetes to which POPs may contribute. When the mechanisms linking diet, obesity and diabetes are assessed, POPs should also be considered.[22] Also, we cannot forget that all of this occurs in specific societies with distinct causal processes for obesity, diabetes and exposure to POPs.[23]

J Epidemiol Community Health 2006;**60**:1006–1008.
doi: 10.1136/jech.2006.053389

Authors' affiliations
Duk-Hee Lee, Department of Preventive Medicine and Health Promotion Research Center, School of Medicine, Kyungpook National University, Daegu, Korea
David R JacobsJr, Division of Epidemiology, School of Public Health, University of Minnesota, Minnesota, USA, and Department of Nutrition, University of Oslo, Oslo, Norway
Miquel Porta, Institut Municipal d'Investigacio Medica, Barcelona, Spain, and School of Medicine, Universitat Autonoma de Barcelona, Barcelona, Spain, and School of Public Health, University of North Carolina at Chapel Hill, USA

Correspondence to: D-H Lee, Department of Preventive Medicine, School of Medicine, Kyungpook National University, 1Ga, Dongin-Dong, Jung-Gu, Daegu 700-422, South Korea; lee_dh@knu.ac.kr

Competing interests: None declared.

REFERENCES

1 **Schafer KS**, Kegley SE. Persistent toxic chemicals in the food supply. *J Epidemiol Community Health* 2002;**56**:813–17.
2 **Institute of Medicine**. *Dioxins and dioxin-like compounds in the food supply. Strategies to decrease exposure*. Washington, DC: The National Academies Press, 2003.

3 **Hansen LG**. Stepping backward to improve assessment of PCB congener toxicities. *Environ Health Perspect* 1998;**106**(Suppl 1):171–89.
4 **Neubert D**. Reflections on the assessment of the toxicity of ''dioxins'' for humans, using data from experimental and epidemiological studies. *Teratog Carcinog Mutagen* 1997–98; **17**:157–215.
5 **Lee DH**, Lee IK, Song K, *et al*. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care* 2006;**29**:1638–44.
6 **Needham LL**, Barr DB, Caudill SP, *et al*. Concentrations of environmental chemicals associated with neurodevelopmental effects in U.S. population. *Neurotoxicology* 2005;**26**:531–45.
7 **Luross JM**, Alaee M, Sergeant DB, *et al*. Spatial distribution of polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Laurentian Great Lakes. *Chemosphere* 2002;**46**:665–72.
8 **Enan E**, Lasley B, Stewart D, *et al*. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) modulates function of human luteinizing granulosa cells via cAMP signaling and early reduction of glucose transporting activity. *Reprod Toxicol* 1996;**10**:191–8.
9 **Olsen H**, Enan E, Matsumura F. Regulation of glucose transport in the NIH 3T3 L1 preadipocyte cell line by TCDD. *Environ Health Perspect* 1994;**102**:454–8.
10 **Enan E**, Matsumura F. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced changes in glucose transporting activity in guinea pigs, mice, and rats in vivo and in vitro. *J Biochem Toxicol* 1994;**9**:97–106.
11 **Remillard RB**, Bunce NJ. Linking dioxins to diabetes: epidemiology and biologic plausibility. *Environ Health Perspect* 2002;**110**:853–8.
12 **Longnecker MP**. Pharmacokinetic variability and the miracle of modern analytical chemistry. *Epidemiology* 2006;**17**:350–1.
13 **Henriksen GL**, Ketchum NS, Michalek JE, *et al*. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. *Epidemiology* 1997;**8**:252–8.
14 **Sweeney MH**, Calvert GM, Egeland GA, *et al*. Review and update of the results of the NIOSH medical study of workers exposed to chemicals contaminated with 2,3,7,8-tetrachlorodibenzodioxin. *Teratog Carcinog Mutagen* 1997–98;**17**:241–7.
15 **Tritscher AM**, Goldstein JA, Portier CJ, *et al*. Dose-response relationships for chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in a rat tumor promotion model: quantification and immunolocalization of CYP1A1 and CYP1A2 in the liver. *Cancer Res* 1992;**52**:3436–42.
16 **Hennig B**, Meerarani P, Slim R, *et al*. Proinflammatory properties of coplanar PCBs: in vitro and in vivo evidence. *Toxicol Appl Pharmacol* 2002;**181**:174–83.
17 **Daneman D**. Type 1 diabetes. *Lancet* 2006;**367**:847–58.
18 **Stumvoll M**, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005;**365**:1333–46.
19 **Hemmings SJ**, Spafford D. Neonatal STZ model of type II diabetes mellitus in the Fischer 344 rat: characteristics and assessment of the status of the hepatic adrenergic receptors. *Int J Biochem Cell Biol* 2000;**32**:905–19.
20 **van den Berg M**, Peterson RE, Schrenk D. Human risk assessment and TEFs. *Food Addit Contam* 2000;**17**:347–58.
21 **Tilson HA**, Kodavanti PR, Mundy WR, *et al*. Neurotoxicity of environmental chemicals and their mechanism of action. *Toxicol Lett* 1998;**102–103**:631–5.
22 **Porta M**. Persistent organic pollutants and the burden of diabetes. *Lancet* 2006;**368**:558–9.
23 **Porta M**. Persistent toxic substances: exposed individuals and exposed populations. *J Epidemiol Community Health* 2004;**58**:534–5.

APHORISM OF THE MONTH

''Establish your own priorities'' (because you wouldn't want anyone to establish them for you, would you?)

You should arrange your own priorities and then begin with the last – the first will then seem less important (for example, sorting mail).

Lowell Levin, JRA