NTP
National Toxicology Program

Environmental Chemicals & Type 1 Diabetes

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National Toxicology Program (NTP)/ Office of Health Assessment and Translation (OHAT)

CHE Partnership call: Type 1 Diabetes and the Environment
November 12, 2014

NTP Workshop "Role of Environmental Chemicals in the Development of Diabetes and Obesity" (January 11-13, 2011)

- Evaluate the science associating exposure to certain chemicals or chemical classes with development of diabetes or obesity in humans

Arsenic	Persistent organic pollutants (POPs)
Bisphenol A (BPA)	Pesticides
Trialkyltins ("Organotins")	Phthalates
Maternal Smoking	Nicotine

- Provide input to NTP and NIEHS for development of a research agenda
- Website: http://ntp.niehs.nih.gov/go/36433

Workshop Conclusions on T1D

- Largely unexplored with respect to potential role of environmental contaminants
  - Vacor, air pollution, nitrates, BPA, maternal smoking
- Traditional toxicology animal studies not particularly useful to identify compounds of interest
  - T1D-related endpoints not assessed
  - Limitations of traditional rodent models to assess
- Unknown utility of Tox21 high throughput screening targets to identify compounds of interest

Review

Role of Environmental Chemicals in Diabetes and Obesity: A National Toxicology Program Workshop Review

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BACKGROUND: There has been increasing interest in the concept that exposures to environmental chemicals may be contributing factors to the epidemics of diabetes and obesity. On 13–15 January 2011, the National Institute of Environmental Health Sciences (NIEHS) Division of the National Toxicology Program (NTP) organized a workshop to evaluate the current state of the science on these topics of increasing public health concern.

OBJECTIVE: The main objective of the workshop was to develop recommendations for a research agenda after completing a critical analysis of the literature for humans and experimental animals exposed to certain environmental chemicals. The environmental exposures considered at the workshop were arsenic, persistent organic pollutants, maternal smoking/nicotine, organotins, phthalates, bisphenol A, and pesticides. High-throughput screening data from Toxicology in the 21st Century (Tox21) were also considered as a way to evaluate potential cellular pathways and generate hypotheses for testing which and how certain chemicals might perturb biological processes related to diabetes and obesity.

CONCLUSIONS: Overall, the review of the existing literature identified linkages between several of the environmental exposures and type 2 diabetes. There was also support for the "developmental obesogen" hypothesis, which suggests that chemical exposures may increase the risk of obesity by altering the differentiation of adipocytes or the development of neural circuits that regulate feeding behavior. The effects may be most apparent when the developmental exposure is combined with consumption of a high-calorie, high-carbohydrate, or high-fat diet later in life. Research on environmental chemical exposures and type 1 diabetes was very limited. This lack of research was considered a critical data gap. In this workshop review, we outline the major themes that emerged from the workshop and discuss activities that NIEHS/NTP is undertaking to address research

obesity has rapidly expanded in the past several years. The White House Task Force on Childhood Obesity (2010), the National Institutes of Health (NIH 2011), and the National Institute of Diabetes and Digestive and Kidney Diseases (2011) all acknowledge the growing science base in this area and cite the need for research to improve understanding of the role of environmental exposures in order to facilitate future prevention strategies. To help develop such a research strategy, the National Institute of Environmental Health Sciences (NIEHS) Division of the National Toxicology Program (NTP) organized a state-of-the-science workshop in January 2011

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Thayer KA et al. 2012. Role of environmental chemicals in diabetes and obesity: A National Toxicology Program workshop report. *Environ Health Perspect* 120(6): 779-789.

OHAT Activities After 2011 Workshop

- Use of existing human data & samples to address research questions
- Help identify hypotheses that could be addressed in targeted research
  - Analyses of high throughput screening data data (ToxCast)
  - ToxRef and CEBS databases queries for animal data

Human Data & Samples

- NHANES
  - Does not distinguish between T1 and T2 diabetes
  - Very small number of cases (based on age at diagnosis as surrogate)
    - 72 cases out of 39,401 observations in NHANES 1999-2006
    - 59 cases when data on adjustment factors is required
  - Screening level associations hard to interpret
    - Most associations were “protective”
      - Real? Complexity associated with compounds that affect the immune system?

Substances Associated with Assumed T1D in NHANES (1999-2006)

CLASS	LABEL	Cases	N Observations	OR (95% CI)
01 - Acrylamide	Glycideamide (pmoL/G Hb)	20	6,812	0.856 (0.733 - 0.999)
07 - Furans	1,2,3,4,7,8-hcxdf (fg/g)	10	4,430	0.378 (0.166 - 0.863)
07 - Furans	1,2,3,4,6,7,8,9-ocdf (fg/g)	9	4,392	0.377 (0.169 - 0.841)
08 - Heavy Metals	Cesium, urine (ng/mL)	18	9,353	0.638 (0.436 - 0.934)
08 - Heavy Metals	Lead, urine (ng/mL)	18	9,354	0.535 (0.317 - 0.905)
08 - Heavy Metals	Tungsten, urine (ng/mL)	17	9,214	0.394 (0.162 - 0.957)
09 - Hydrocarbons	3-fluorene (ng/L)	3	2,504	0.551 (0.335 - 0.908)
09 - Hydrocarbons	2-phenanthrene (ng/L)	3	2,500	0.042 (0.003 - 0.506)
11 - Nutrients	Vitamin A (ug/dL)	48	22,269	0.726 (0.598 - 0.881)
11 - Nutrients	Retinyl stearate (ug/dL)	47	21,004	1.544 (1.152 - 2.069)
11 - Nutrients	Gamma tocopherol (ug/dL)	48	22,011	1.709 (1.027 - 2.842)
11 - Nutrients	Lutein(ug/dL)	18	6,788	0.659 (0.458 - 0.949)
11 - Nutrients	Zeaxanthin(ug/dL)	18	6,788	0.447 (0.254 - 0.787)
11 - Nutrients	cis- Lutein/Zeaxanthin(ug/dL)	18	6,788	0.561 (0.369 - 0.852)
12 - Organochlorine Pesticides	Mirex (ng/g)	7	3,584	1.54 (1.043 - 2.276)
13 - Polychlorinated Biphenyls	PCB28 (ng/g)	7	3,305	0.306 (0.122 - 0.768)
13 - Polychlorinated Biphenyls	PCB99 (ng/g)	13	5,403	0.287 (0.125 - 0.658)
13 - Polychlorinated Biphenyls	PCB101 (ng/g)	13	5,467	0.558 (0.377 - 0.824)
13 - Polychlorinated Biphenyls	PCB138 (ng/g)	13	5,454	0.248 (0.097 - 0.631)
13 - Polychlorinated Biphenyls	PCB153 (ng/g)	13	5,463	0.272 (0.093 - 0.794)
13 - Polychlorinated Biphenyls	PCB177 (ng/g)	13	5,388	0.492 (0.271 - 0.891)
13 - Polychlorinated Biphenyls	PCB183 (ng/g)	13	5,453	0.506 (0.284 - 0.902)
13 - Polychlorinated Biphenyls	PCB105 (ng/g)	13	5,438	0.522 (0.311 - 0.879)
13 - Polychlorinated Biphenyls	PCB118 (ng/g)	13	5,455	0.157 (0.054 - 0.454)
17 - Phthalates	Mono-cyclohexyl phthalate (ng/mL)	16	9,566	0.377 (0.173 - 0.817)
18 - Polybrominated Ethers	2,4,4'-tribromodiphenyl ether	5	1,851	0.193 (0.07 - 0.533)
18 - Polybrominated Ethers	2,3',4,4'-tetrabromodiphenyl ether	5	1,862	0.046 (0.008 - 0.263)
18 - Polybrominated Ethers	2,2',4,4',5-pentabromodiphenyl ether	5	1,846	0.491 (0.269 - 0.897)
18 - Polybrominated Ethers	2,2',4,4',5,5'-hexabromodiphenyl ether	5	1,899	0.304 (0.155 - 0.596)
19 - Polyflourochemicals	Perfluorohexane sulfonic acid	7	3,956	0.438 (0.244 - 0.786)
19 - Polyflourochemicals	Perfluorooctanoic acid	7	3,956	0.553 (0.33 - 0.926)
19 - Polyflourochemicals	Perfluorooctane sulfonamide	7	3,956	2.088 (1.1 - 3.963)
21 - Volatile Compounds	Blood Chloroform (pg/ml)	16	5,015	0.534 (0.337 - 0.847)
91 - Fungicides	Pentachlorophenol (ug/L)	17	6,634	1.529 (1.029 - 2.272)

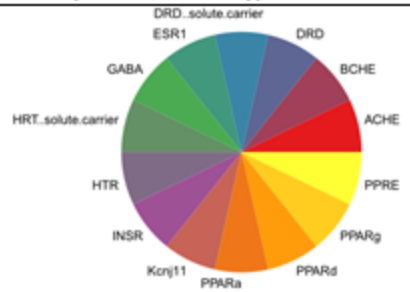
Human Data & Samples

- Access existing samples
  - The Environmental Determinants of Diabetes in the Young (TEDDY),SEARCH for Diabetes in Youth (SEARCH), Environmental Determinants of Islet Autoimmunity (ENDIA)
    - We are collaborating on speciated arsenic analysis using plasma samples from SEARCH case-controls
  - “Environment” in these studies mostly limited to diet and nutrition
  - Sample availability and lack of focused hypotheses are limitations
    - Often <0.5 ml serum available for analysis
    - Collection procedures not ideal for phenols and phthalates
  - Animal data often not compelling enough to support getting samples
- National Children’s Study
  - Likely underpowered for T1D based on NHANES prevalence
  - Future unclear, slow pace

ToxCast

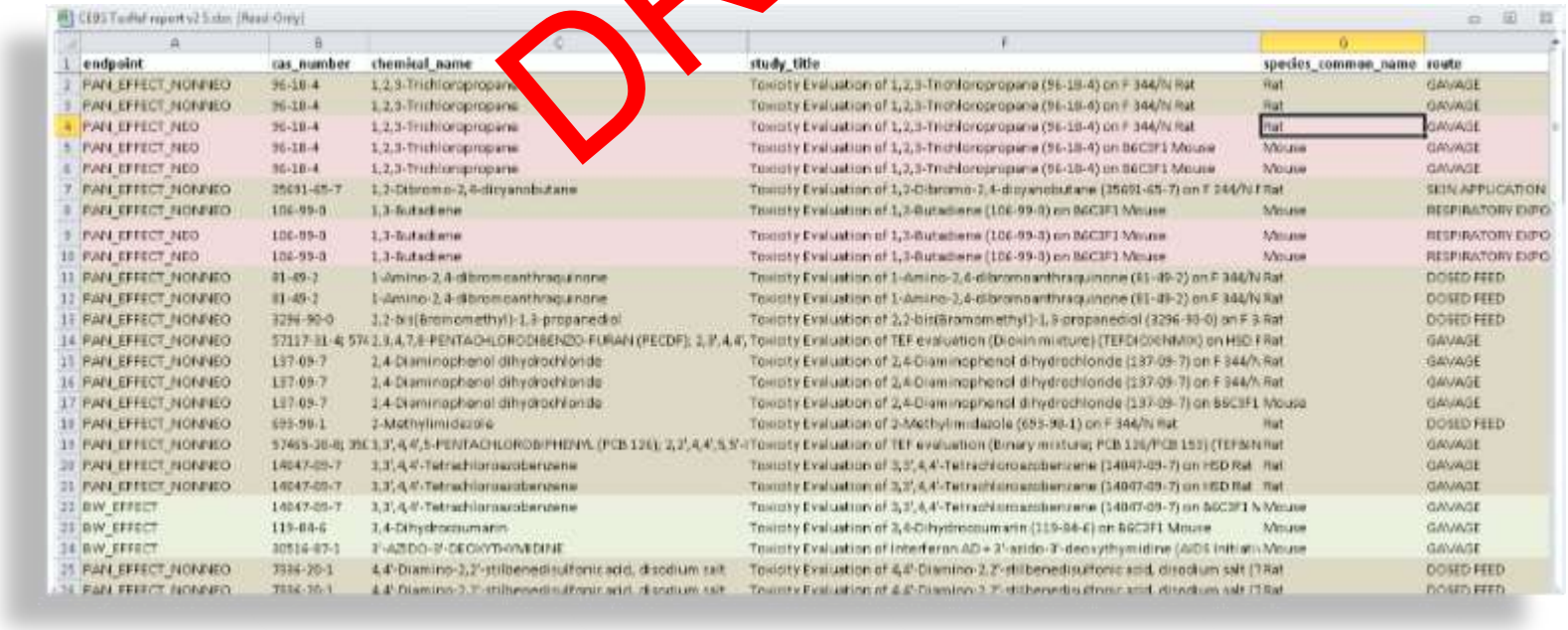
- Developed ToxPis with experts from 2011 workshop
  - Biological processes: Islet cell function, insulin sensitivity, feeding behavior, adipocyte differentiation
  - Focused on ToxCast rather than Tox21 platform because it has more assay coverage of relevant targets
- Highest ranking environmental compounds do not overlap with those implicated in peer-reviewed literature
- No or very limited data available to evaluate for context of findings
- Manuscript close to submission (using most recent ToxCast data, Phase 2 of 1858 compounds released in October 2014)

Top 30 of 1855 chemicals tested in Phase 2 ToxCast in Morris White's ToxPi model

Rank	Islet Cell Function (Alison Holloway)	Islet Cell Function (Morris WHite)
		
1	**Isopropyl triethanolamine titanate [CAS 36673-16-2]** 0.182 Use: coupling agent Class: organometallic amine silicate	**2-Ethylhexyl diphenyl phosphate [CAS 1241-94-7]** 0.173 Use: plasticizer/fireproofing Class: phenol
2	**Auramine hydrochloride [CAS 2465-27-2]** 0.161 Use: dye/disinfectant Class: aniline	**Isopropyl triethanolamine titanate [CAS 36673-16-2]** 0.167 Use: coupling agent Class: organometallic amine silicate
3	**Bifenazate [CAS 149877-41-8]** 0.133 Use: insecticide Class: Not Assigned phenyl-phenyl alkoxy carbamate	**Auramine hydrochloride [CAS 2465-27-2]** 0.157 Use: dye/disinfectant Class: aniline aniline-aniline [CN] alkylate
4	**Fenpyroximate (Z,E) [CAS 111812-58-9]** 0.1[illegible] Use: insecticide Class: phenyl-pyrazole [O] benzoate	**1-Cedr-8-en-9-ylethanone [CAS 32388-55-9]** 0.106 Use: flavor and fragrance agent Class: ketone
5	**2-Chloro-N-phenylacetamide [CAS 87-65-5]** 0.124 Use: EPA inert (pesticides) Class: phenyl acetanilide halide	**Pyridate [CAS 55512-33-9]** 0.092 Use: herbcide Class: diazine carboxylate halide sulfide
6	**4,4'-Methylenebis(2,6-diethylaniline) [CAS 13680-35-8]** 0.108 Use: chemcal reactant Class: aniline	**Tributyltin benzoate [CAS 4342-36-3]** 0.091 Use: microbicide Class: organometallic organometallic
7	**Bis(2-ethylhexyl) phosphate [CAS 298-07-7]** 0.107 Use: chemcal additive Class: phosphate alkyl	**o,p'-DDD [CAS 53-19-0]** 0.091 Use: pesticide degradate and impurity; pharmaceutical Class: phenyl chloro
8	**2-Mercaptobenzothiazole [CAS 149-30-4]** 0.106 Use: rubber additive Class: thiobenzimidazole	**2-Methylaniline hydrochloride [CAS 636-21-5]** 0.091 Use: chemcal intermediate Class: aniline
9	**Isoxaben [CAS 82558-50-7]** 0.106 Use: herbcide Class: phenyl-oxazole [CON] alkoxy	**4-Nitrotoluene [CAS 99-99-0]** 0.089 Use: chemcal reactant Class: phenyl nitro
10	**1,4-Diaminoanthraquinone [CAS 128-95-0]** 0.103 Use: dye Class: anthraquinone	**Tannic acid [CAS 1401-55-4]** 0.082 Use: natural product Class: phenol benzoic acid

NTP's CEBS and EPA's ToxRef Databases

- Query NTP's CEBS and EPA's ToxRef animal study databases for chemicals that cause pancreatic toxicity and have immune effects
- Analysis underway
- Initial assessment that compounds of interest do not overlap with those implicated in peer-reviewed literature



endpoint	cas_number	chemical_name	study_title	species_common_name	route
PAN_EFFECT_NONNEO	96-18-4	1,2,3-Trichloropropane	Toxicity Evaluation of 1,2,3-Trichloropropane (96-18-4) on F 344/N Rat	Rat	GAVAGE
PAN_EFFECT_NONNEO	96-18-4	1,2,3-Trichloropropane	Toxicity Evaluation of 1,2,3-Trichloropropane (96-18-4) on F 344/N Rat	Rat	GAVAGE
PAN_EFFECT_NEO	96-18-4	1,2,3-Trichloropropane	Toxicity Evaluation of 1,2,3-Trichloropropane (96-18-4) on F 344/N Rat	Rat	GAVAGE
PAN_EFFECT_NEO	96-18-4	1,2,3-Trichloropropane	Toxicity Evaluation of 1,2,3-Trichloropropane (96-18-4) on B6C3F1 Mouse	Mouse	GAVAGE
PAN_EFFECT_NEO	96-18-4	1,2,3-Trichloropropane	Toxicity Evaluation of 1,2,3-Trichloropropane (96-18-4) on B6C3F1 Mouse	Mouse	GAVAGE
PAN_EFFECT_NONNEO	35691-65-7	1,2-Dibromo-2,4-dicyanobutane	Toxicity Evaluation of 1,2-Dibromo-2,4-dicyanobutane (35691-65-7) on F 344/N F	Rat	SKIN APPLICATION
PAN_EFFECT_NONNEO	106-99-0	1,3-Butadiene	Toxicity Evaluation of 1,3-Butadiene (106-99-0) on B6C3F1 Mouse	Mouse	RESPIRATORY EXPO
PAN_EFFECT_NEO	106-99-0	1,3-Butadiene	Toxicity Evaluation of 1,3-Butadiene (106-99-0) on B6C3F1 Mouse	Mouse	RESPIRATORY EXPO
PAN_EFFECT_NONNEO	106-99-0	1,3-Butadiene	Toxicity Evaluation of 1,3-Butadiene (106-99-0) on B6C3F1 Mouse	Mouse	RESPIRATORY EXPO
PAN_EFFECT_NONNEO	81-49-2	1-Amino-2,4-dibromoanthraquinone	Toxicity Evaluation of 1-Amino-2,4-dibromoanthraquinone (81-49-2) on F 344/N	Rat	DOSED FEED
PAN_EFFECT_NONNEO	81-49-2	1-Amino-2,4-dibromoanthraquinone	Toxicity Evaluation of 1-Amino-2,4-dibromoanthraquinone (81-49-2) on F 344/N	Rat	DOSED FEED
PAN_EFFECT_NONNEO	3296-90-0	2,2-bis(Bromomethyl)-1,3-propanediol	Toxicity Evaluation of 2,2-bis(Bromomethyl)-1,3-propanediol (3296-90-0) on F 3	Rat	DOSED FEED
PAN_EFFECT_NONNEO	57117-31-4; 57	2,3,4,7,8-PENTACHLORODIBENZO-FURAN (PECDF); 2,3',4,4',	Toxicity Evaluation of TEF evaluation (Dioxin mixture) (TEFDIOXMIX) on HSD F	Rat	GAVAGE
PAN_EFFECT_NONNEO	137-09-7	2,4-Diaminophenol dihydrochloride	Toxicity Evaluation of 2,4-Diaminophenol dihydrochloride (137-09-7) on F 344/N	Rat	GAVAGE
PAN_EFFECT_NONNEO	137-09-7	2,4-Diaminophenol dihydrochloride	Toxicity Evaluation of 2,4-Diaminophenol dihydrochloride (137-09-7) on F 344/N	Rat	GAVAGE
PAN_EFFECT_NONNEO	137-09-7	2,4-Diaminophenol dihydrochloride	Toxicity Evaluation of 2,4-Diaminophenol dihydrochloride (137-09-7) on B6C3F1	Mouse	GAVAGE
PAN_EFFECT_NONNEO	693-98-1	2-Methylimidazole	Toxicity Evaluation of 2-Methylimidazole (693-98-1) on F 344/N Rat	Rat	DOSED FEED
PAN_EFFECT_NONNEO	57465-28-8; 35	3,3',4,4',5-PENTACHLOROBIPHENYL (PCB 126); 2,3',4,4',5,5'-	Toxicity Evaluation of TEF evaluation (Binary mixture; PCB 126/PCB 153) (TEFSIN	Rat	GAVAGE
PAN_EFFECT_NONNEO	14047-09-7	3,3',4,4'-Tetrachloroazobenzene	Toxicity Evaluation of 3,3',4,4'-Tetrachloroazobenzene (14047-09-7) on HSD Rat	Rat	GAVAGE
PAN_EFFECT_NONNEO	14047-09-7	3,3',4,4'-Tetrachloroazobenzene	Toxicity Evaluation of 3,3',4,4'-Tetrachloroazobenzene (14047-09-7) on HSD Rat	Rat	GAVAGE
BW_EFFECT	14047-09-7	3,3',4,4'-Tetrachloroazobenzene	Toxicity Evaluation of 3,3',4,4'-Tetrachloroazobenzene (14047-09-7) on B6C3F1 M	Mouse	GAVAGE
BW_EFFECT	119-84-6	3,4-Dihydrocoumarin	Toxicity Evaluation of 3,4-Dihydrocoumarin (119-84-6) on B6C3F1 Mouse	Mouse	GAVAGE
BW_EFFECT	30516-87-1	3'-AZIDO-3'-DEOXYTHYMIDINE	Toxicity Evaluation of Interferon AD + 3'-azido-3'-deoxythymidine (AIDS Initiati	Mouse	GAVAGE
PAN_EFFECT_NONNEO	7336-20-1	4,4'-Diamino-2,2'-stilbenedisulfonic acid, disodium salt	Toxicity Evaluation of 4,4'-Diamino-2,2'-stilbenedisulfonic acid, disodium salt (T	Rat	DOSED FEED
PAN_EFFECT_NONNEO	7336-20-1	4,4'-Diamino-2,2'-stilbenedisulfonic acid, disodium salt	Toxicity Evaluation of 4,4'-Diamino-2,2'-stilbenedisulfonic acid, disodium salt (T	Rat	DOSED FEED

Assessment of Background Work

- We may be missing the mark by focusing on chemicals implicated in current literature, e.g., BPA
  - BUT, hypotheses based on animal or HTS data might not be compelling enough to compete for human T1D samples
- Need to consider how to interpret associations in human studies that appear “protective” in nature