

1 **Role of Environmental Chemicals in Diabetes and Obesity: A**
2 **National Toxicology Program Workshop Report**

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38

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43

44 **Contributors**

45 Michael A. Gallo served as workshop Chair and Kris Thayer was lead in organizing the meeting
46 and assembling background materials. Jerry Heindel and John Bucher were NIEHS/DNTP staff
47 extensively involved in organizing the meeting. Members of specific breakout groups are
48 described in the background materials for the meeting at <http://DNTP.niehs.nih.gov/go/36433>,
49 see “List of Breakout Group Members.”

50 **Conflict of interest**

51 The authors declare they have no actual or potential competing financial interests.

52

53 **Abbreviations**

54 As – arsenic

55 BMI – body mass index

56 BPA– bisphenol A

57 DDE – dichlorodiphenyldichloroethylene [1,1-*bis*-(4-chlorophenyl)-2,2-dichloroethene]

58 DDT – dichlorodiphenyltrichloroethane [1,1-*bis*-(4-chlorophenyl)-2,2,2-trichloroethane]

59 DEHP – di(2-ethylhexyl) phthalate

60 DERT – Division of Extramural Research and Training

61 DIR – Division of Intramural Research

62 DNTP – Division of the National Toxicology Program

63 EPA – U.S. Environmental Protection Agency

64 ERR γ – estrogen-related receptor γ

65 FDA – U.S. Food and Drug Administration

66 GABA – gamma-aminobutyric acid

67 HOMA – homeostatic model assessment

- 68 HOMA-IR – homeostatic model assessment-insulin resistance
- 69 HTS – high throughput screening
- 70 med – median
- 71 MEP – monoethyl phthalate
- 72 MEHP – mono(2-ethylhexyl) phthalate
- 73 NCTR – FDA National Center for Toxicological Research
- 74 NHGRI – National Human Genome Research Institute
- 75 NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases
- 76 NIEHS – National Institute of Environmental Health Sciences
- 77 PCBs – polychlorinated biphenyls
- 78 PNU – N-3-pyridylmethyl N'-p-nitrophenyl urea
- 79 POPs – persistent organic pollutants
- 80 ppb – parts per billion
- 81 ppm – parts per million
- 82 PPARs – peroxisome proliferator-activated receptors
- 83 PVC – polyvinyl chloride
- 84 OR – odds ratio
- 85 RXR – retinoid X receptor
- 86 T1D – type 1 diabetes
- 87 T2D – type 2 diabetes
- 88 TBT – tributyltin
- 89 TCDD – dioxin
- 90 ToxCast™ – US EPA ToxCast™ Database (<http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp>)

91 ToxRefDB – US EPA Toxicity Reference Database (<http://www.epa.gov/ncct/toxrefdb/>)

92

93 **ABSTRACT**

94 **Background:** There has been increasing interest in the concept that exposures to environmental
95 chemicals may be contributing factors to the epidemics of diabetes and obesity. On January 11-
96 13, 2011 the National Toxicology Program (DNTP) organized a workshop to evaluate the current
97 state of the science on these topics of increasing public health concern.

98 **Objective:** The main objective of the workshop was to develop recommendations for a research
99 agenda following a critical analysis of literature reports for humans and experimental animals
100 exposed to certain environmental chemicals. The chemicals, or chemical classes, considered at
101 the workshop were arsenic, persistent organic pollutants (POPS), maternal smoking/nicotine,
102 organotins, phthalates, bisphenol A, and pesticides. High throughput screening data from Tox21
103 was also considered as a way to evaluate potential cellular pathways and generate hypotheses for
104 testing how certain chemicals might perturb biological processes related to diabetes and obesity.

105 **Conclusions:** Overall, the review of the existing literature identified several linkages of
106 exposures to certain chemicals or chemical classes with type 2 diabetes. There was also support
107 for the “developmental obesogen” hypothesis which suggests that chemicals may act to alter the
108 differentiation of adipocytes or development of neural circuits that regulate feeding behavior to
109 result in a predisposition to obesity and related metabolic disorders, especially under the
110 influence of high-calorie, high fat diets. Very little research was found directed towards
111 understanding associations of environmental chemical exposures with type 1 diabetes. This lack
112 of research was considered a critical data gap. This workshop report outlines the major themes
113 emerging from the workshop and discusses activities that NIEHS and DNTP are undertaking to

114 address research recommendations. This report also serves as the introduction to a series of
115 papers that describe in more detail the critical assessment of the literature provided by the
116 workshop participants.

117

118 **INTRODUCTION**

119 Diabetes and obesity are major epidemics in the US and abroad. Based on data from 2005-2008,
120 25.6 million, or 11.3%, of all people in the US aged ≥ 20 years have diagnosed or undiagnosed
121 diabetes (CDC 2011). The total direct medical costs and indirect costs (disability, work loss,
122 premature death) associated with diabetes in the US during 2007 was \$174 billion (CDC 2011).
123 Another 35% of people in this age category have pre-diabetes, a condition where blood glucose
124 is higher than normal but not high enough to be classified as diabetes. Diabetes is being
125 diagnosed in individuals earlier in life as well. Being overweight or obese are well-known risk
126 factors for the development of type 2 diabetes, perhaps accounting for $\sim 70\%$ of cases (Eyre et al.
127 2004). The prevalence of obesity worldwide had doubled since 1980 (WHO 2011). In the US,
128 the prevalence of obesity among children and adolescents aged 2-19 years has almost tripled
129 since 1980 and an estimated 16.9%, or 12.5 million, of children and adolescents are considered
130 obese (Ogden and Carroll 2010). This trend is also apparent in preschool children aged 2-5
131 years, where obesity increased from 5% in 1976-1980 to 10.4% in 2007-2008 (Ogden and
132 Carroll 2010).

133

134 Excess caloric consumption and a sedentary lifestyle are well-recognized risk factors for obesity
135 and diabetes. However, there is growing consideration of “non-traditional” risk factors (e.g.,
136 environmental chemicals, stress, micronutrients, gut *microbiome*) as contributors in the etiology
137 of these health conditions. Research addressing the role of environmental chemicals in diabetes
138 and obesity has rapidly expanded in the past several years. The May 2010 White House Task

139 Force on Childhood Obesity (2010), the March 2011 NIH Strategic Plan for Obesity (2011), and
140 the February 2011 Diabetes Strategic Plan from the National Institute of Diabetes and Digestive
141 and Kidney Diseases (NIDDK 2011) all acknowledge the growing science base in this area and
142 cite the need to understand more about the role of environmental exposures as part of future
143 research and prevention strategies. To help develop such a research strategy the National
144 Toxicology Program (DNTP) organized a state-of-the-science workshop in January 2011 entitled
145 [“Role of Environmental Chemicals in the Development of Diabetes and Obesity”](#) to evaluate the
146 literature in terms of its evidence concerning associations between certain chemicals and risk of
147 diabetes and/or obesity. The specific chemicals or chemical classes evaluated were arsenic,
148 maternal smoking during pregnancy/nicotine, organic tin compounds (“organotins”), phthalates,
149 bisphenol A, pesticides, and various persistent organic pollutants. These are all chemicals or
150 chemical classes that had been linked to these diabetes and/or obesity in the literature. A diverse
151 group of more than 50 scientists including endocrinologists, toxicologists, epidemiologists,
152 bioinformaticists as well as experts in the pathobiology of diabetes and obesity were asked to
153 consider the current literature for consistency and biological plausibility, with the ultimate goal
154 of providing advice to the NIEHS/DNTP in developing a research agenda on these emerging
155 topics. Literature review documents, meeting presentations, and other background materials for
156 the workshop are available at <http://DNTP.niehs.nih.gov/go/36433>.

157

158 Overall, the existing literature was judged to provide plausibility, varying from suggestive to
159 strong, that exposure to environmental chemicals may contribute to the epidemic of diabetes
160 and/or obesity. This workshop report provides an overview of the major themes emerging from
161 the workshop and describes several activities that NIEHS and DNTP are undertaking to address

162 research recommendations. This report also serves as the announcement of an upcoming series of
163 papers to be published in *Environmental Health Perspectives* describing in more detail the
164 critical assessment of the literature provided by the workshop participants.

165 **WORKSHOP FORMAT AND LITERATURE SEARCH STRATEGY**

166 The workshop format was an introductory plenary session and a series of breakout group
167 meetings, followed by plenary sessions to disseminate and discuss the findings from individual
168 breakout group deliberations. A series of white papers was distributed prior to the workshop to
169 help focus discussion. For the individual chemicals or chemical classes, workshop participants
170 were asked to (1) evaluate the strength/weaknesses, consistency, and biological plausibility of
171 findings reported in humans and experimental animals, (2) identify the most useful and relevant
172 endpoints in experimental animals, *in vitro* models, and screening systems to assess these
173 diseases, and (3) identify data gaps and areas for future evaluation/research. Data from the
174 Toxicology in the 21st Century high throughput screening initiative (“Tox21”) was also
175 considered during the meeting. Experts used the data, primarily derived from Phase I of
176 ToxCast™, to help evaluate biological plausibility as well as to develop testable predictions of
177 which chemicals might perturb biological processes related to diabetes and obesity. Experts were
178 also asked to suggest relevant assay targets that could be included in Tox21 in the future to better
179 screen for perturbations of biological processes involved in diabetes and obesity.

180

181 Obesity is a major risk factor for metabolic syndrome and subsequent type 2 diabetes. In the
182 context of this workshop, there was no clear or consistent distinction between these health
183 outcomes, and they were considered collectively across the various chemicals or chemical

184 classes considered. For some exposures, such as maternal smoking/nicotine, organotins and
185 bisphenol A, obesity has been studied as a primary health outcome. For arsenic and POPs the
186 focus was on diabetes, and obesity was considered as a potential confounding or modifying
187 factor.

188

189 A PubMed search strategy was developed to identify studies for xenobiotic exposures related to
190 diabetes and obesity using both a MeSH-based and a keyword strategy (see Supplemental
191 Material). The keyword search identifies “new” articles that were not yet indexed in PubMed.
192 Additional details about the articles considered relevant from this search and those that were
193 “hand collected” during the course of preparing the background documents will be presented in
194 subsequent publications dealing with specific chemicals.

195

196 Findings from all the human studies were summarized in an Excel file. This document can be
197 used in conjunction with a new graphical display program referred to as the Metadata Viewer, a
198 tool to help the research community search the existing epidemiological studies. In brief, the
199 graphing program allows the user to structure queries to look at main findings for a variety of
200 variables or combination of variables (e.g., chemical class, specific chemical, chemical by health
201 outcome, etc.). Data can also be grouped or sorted in order to conduct more detailed assessments
202 of patterns of findings. The presentation format for human studies is a “forest plot” graphical
203 display as shown in Figures 1-3. The input data file for the diabetes/obesity workshop contains
204 almost 800 main findings. This software program was used in the workshop to visually display
205 data but was not used to conduct quantitative meta-analyses. The graphing program,

206 accompanying data file, and instructions for use are publically accessible at
207 <http://DNTP.niehs.nih.gov/tools/MetaDataViewer/>.

208 **MAJOR FINDINGS**

209 **Maternal smoking and nicotine**

210 The strongest conclusion from the workshop was that nicotine likely acts as a developmental
211 obesogen in humans. This conclusion was based on the very consistent pattern of
212 overweight/obesity observed in epidemiology studies of children of mothers who smoked during
213 pregnancy (**Figure 1**) and was supported by findings from laboratory animals exposed to
214 nicotine during prenatal development. Crude and adjusted odd ratios (ORs) were similar in the
215 epidemiological studies suggesting that social and behavioral differences between smokers and
216 non-smokers are not likely to account for the observed differences in overweight risk (Oken et al.
217 2008). Two recent meta-analyses used funnel plot methods to ascertain publication bias and
218 concluded there was some evidence for publication bias, but not enough to negate the overall
219 conclusion of increased risk (Ino 2010; Oken et al. 2008). The metabolic changes reported in the
220 animal studies recapitulated “to a large extent” those seen in children of mothers who smoke.
221 The breakout group recognized that other components in cigarette smoke may also be
222 contributing to the association between maternal smoking and childhood overweight/obesity;
223 however the studies of nicotine in experimental animals provided compelling evidence that
224 nicotine alone was the causal agent.

225 **Arsenic**

226 The workgroup that evaluated this literature concluded there was suggestive evidence for an
227 association of diabetes with living in regions with relatively high environmental arsenic
228 exposures (> 150 ppb) in drinking water (**Figure 2**). However, additional research is needed to
229 determine whether the strength of the association establishes a contributory or causal
230 relationship. The current literature was considered to provide “insufficient” evidence for an
231 association with diabetes and arsenic in lower exposure areas (<150 ppb) in drinking water,
232 although recent studies with better measures of exposure and outcome provided increased
233 evidence for an association.

234

235 The literature on arsenic and diabetes in experimental animals was judged inconclusive, but
236 findings from newer animal studies provide findings that are consistent with the human results.
237 The body of existing studies is highly diverse, with considerable variation in the duration of
238 treatment (one day to two years), routes of administration, and dose levels used in the studies. Most
239 of the studies treated animals with sodium arsenite, As(III), or arsenic trioxide, but other
240 arsenicals have also been studied (Aguilar et al. 1997; Arnold et al. 2003; Hill et al. 2009; Paul et
241 al. 2008). The studies also vary in experimental design and model systems used to assess
242 endpoints relevant to diabetes as a health effect. Most of the studies were not designed to
243 examine the diabetogenic effects of chronic arsenic exposure. Although the literature as a whole
244 was judged inconclusive, findings from recent studies that were designed to focus more
245 specifically on diabetes appear consistent with those human studies that link arsenic exposure to
246 diabetes. Supportive findings include impaired glucose tolerance in studies with mice or rats
247 treated with As(III) for periods of several months at drinking water concentrations ranging from
248 to 5 to 50 ppm (Cobo and Castineira 1997; Paul et al. 2008; Paul et al. 2007; Wang et al. 2009).

249 Measures of insulin regulation may also be affected, i.e., increased HOMA-IR, by oral gavage
250 treatment of Wistar rats with As(III) at a dose of 3.4 mg/kg bw/day for 90 days (Izquierdo-Vega
251 et al. 2006) or treatment of pregnant female LM/ Bc/Fnn mice with 9.6 mg/kg As(V) by ip
252 injection on gestational days 7.5 and 8.5 (Hill et al. 2009).

253

254 Most *in vitro* or mechanistic studies were not designed specifically to study the diabetogenic or
255 adipogenic effects of arsenic. Nevertheless, these studies suggest several pathways by which
256 arsenic could influence pancreatic β -cell function and insulin sensitivity, including oxidative
257 stress, effects on glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and
258 Ca^{2+} signalling [reviewed in Tseng (2004), Diaz-Villasenor et al. (2007; 2008), Druwe (2010)].
259 Studies suggest that arsenic may exert negative effects on β -cell function *in vitro* through several
260 mechanisms depending on the concentration tested (Fu et al. 2010).

261 **Epidemiological studies of Persistent Organic Pollutants (POPs) and Diabetes**

262 Persistent organic pollutants (POPs) consists of broad classes organohalides (i.e.,
263 organochlorines, organofluorines, and organobromines). The POPs literature related to diabetes
264 is quite varied in quality and complexity. It consists of almost 100 epidemiological studies that
265 report ~500 findings relating to pathways and signs of diabetes or metabolic syndrome. Often
266 results for multiple POPs are reported in the same study. The workgroup developed a rating for
267 each of these studies based on study design and the strategy used to assess exposure and the
268 health outcome. Studies were considered less useful if the diagnoses of diabetes came from death
269 certificates, if diabetes was self-reported, if exposure was self-reported, or if exposure was not
270 clearly measured. The breakout group then used the Metadata Viewer program to assess patterns

271 of association between various chemicals or chemical classes and diabetes (Boyles et al. in
272 press).

273

274 The workgroup concluded that there is evidence for a positive association of diabetes with
275 certain organochlorine POPs based on collected analyses of cross-sectional,
276 prospective/retrospective cohort, and occupational exposure studies. Initial data mining
277 indicates strongest correlations of diabetes with trans-nonachlor, DDE/DDT, and
278 dioxins/dioxin-like chemicals including PCBs (see **Figure 3** for PCB findings). In no case was
279 the data considered sufficient to establish causality. The very strong exposure correlations
280 among some POPs (correlation coefficients of 0.50-0.90) make it difficult to identify individual
281 POPs as potential causal agents.

282 **Organotins and Phthalates (PPAR Activators)**

283 Organotins and phthalates were considered together in a breakout group session because these
284 classes both interact with peroxisome proliferator-activated receptors (PPARs). The PPARs are
285 intimately involved in the regulation of adipocyte differentiation, production of adipokines
286 (immunomodulatory proteins secreted by adipose tissue), metabolic syndrome, and insulin
287 sensitivity (Janesick A 2011; Kahn and McGraw 2010; Li et al. 2011; Wang 2010). In addition,
288 there is the potential for co-exposures to these two chemical classes as they have a common use
289 as plasticizers in polyvinylchloride (PVC) plastics. The extent and magnitude of exposure is
290 assumed to be higher for phthalates but exposure to organotins is not well characterized.

291

292 The pattern of stimulatory activity varies for specific PPAR receptor subtypes between the
293 organotins (primarily TBT) and individual phthalates with the organotins appearing to have a
294 stronger mechanistic profile for inducing “obesogenic” effects. The organotins are agonists for
295 PPAR γ as well as RXR α , two receptors known to have positive effects on adipocyte
296 differentiation *in vitro* when activated (Grun et al. 2006; Hiromori et al. 2009; Inadera and
297 Shimomura 2005; Kanayama et al. 2005; le Maire et al. 2009; Nakanishi et al. 2005; Nishikawa
298 et al. 2004). Because PPAR γ and RXR α heterodimerize, these compounds will stimulate both
299 parts of the complex.

300

301 The phthalates are less potent activators of PPAR γ compared to organotins with agonist activity
302 occurring at a 1000x higher concentrations (~10-100 μ M versus ~10-100 nM) and they have not
303 been identified as agonists for RXR α . In contrast, the phthalates are more potent agonists for
304 PPAR α compared to PPAR γ . In rodent models, PPAR α appears to mediate high dose di(2-
305 ethylhexyl) phthalate (DEHP)-induced body weight loss, and its role in regulating adipogenesis
306 is less clear. The organotins are not considered activators of PPAR α (personal communication
307 with Bruce Blumberg, November 28, 2010).

308 *Organotins*

309 There are no epidemiological studies of organotin exposure and obesity or diabetes. There are
310 poisoning incident reports, mostly in workers involved in applying the compounds for pesticide
311 use, that describe incidents of hyperglycemia and/or glycosuria [(Colosio et al. 1991; Manzo et
312 al. 1981), reviewed in NIOSH Criteria Document for Organotin Compounds (1976)]. Recent
313 animal and mechanistic studies report stimulatory effects of TBT on adipocyte differentiation (*in*

314 *vitro* and *in vivo*) and increased amount of fat tissue (i.e., larger epididymal fat pads) in adult
315 animals exposed to TBT during fetal life (Grun and Blumberg 2006; Hiromori et al. 2009;
316 Inadera and Shimomura 2005; Kanayama et al. 2005; Kirchner et al. 2010; Nakanishi et al.
317 2005). *In vitro* effects of TBT include increased lipid accumulation in adipocytes and the
318 promotion of multipotent stromal stem cells to differentiate into adipocytes [(Kirchner et al.
319 2010). Although the organotins “obesogen” literature is relatively new, with few studies, the
320 quality of the existing studies was considered high by the breakout group.

321 *Phthalates*

322 Three cross-sectional human studies of exposure to phthalates were discussed by the breakout
323 group (Boas et al. 2010; Hatch et al. 2008; Stahlhut et al. 2007). These studies report some
324 positive associations but did not provide sufficient evidence to conclude there is an association
325 with diabetes or obesity. Rather, the epidemiology studies were considered exploratory with
326 preliminary data suggesting the possibility of gender differences in associations, and that
327 different phthalates may have different activities. In these studies the urinary phthalate
328 metabolite mono-ethyl phthalate (MEP) was most often associated with higher BMI (Hatch et
329 al. 2008), waist circumference (Stahlhut et al. 2007), or HOMA (Stahlhut et al. 2007). This
330 observation was interesting because MEP is generally considered inactive with respect to the
331 anti-androgen effects of phthalates. Mono-2-ethylhexyl phthalate (MEHP) was associated with
332 decreased BMI in females older than 12 years (Hatch et al. 2008).

333

334 Understanding differences in activity for PPAR α between humans and rodents is important with
335 respect to understanding potential effects of phthalates on body weight and metabolic endpoints.

336 Animals treated with relatively high doses of phthalates, such as DEHP, typically display
337 decreased body weight and fat mass (Itsuki-Yoneda et al. 2007; Sakurai et al. 1978) and these
338 effects appear to be largely mediated via the PPAR α agonist activities of DEHP metabolites
339 (Feige et al. 2010; Martinelli et al. 2010). The effects on decreased body weight and fat mass
340 were present in wild type mice, but not PPAR α knockout mice, demonstrating the importance of
341 PPAR α in regulating the fat loss (Feige et al. 2010). However, Feige et al. (2010) also assessed
342 the effects of DEHP in genetically modified mice in which the normal mouse PPAR α gene was
343 replaced with the human gene. In the humanized model, mice treated with DEHP gained more
344 weight and had an increase in epididymal white adipose mass compared to the wild-type
345 animals. While PPAR γ in rodents and humans acts similarly, PPAR α activity in the rodent
346 model is stronger compared to humans and may mask effects mediated through PPAR γ .

347 **Bisphenol A (BPA)**

348 Overall, this breakout group concluded that the existing data, primarily based on animal and *in*
349 *vitro* studies, are suggestive of an effect of BPA on glucose homeostasis, insulin release and
350 cellular signalling in pancreatic β -cells, and adipogenesis (Alonso-Magdalena et al. 2010;
351 Miyawaki et al. 2007; Ryan et al. 2010; Somm et al. 2009). The existing human data on diabetes
352 (Lang et al. 2008; Melzer et al. 2010) or as a developmental obesogen (Padmanabhan et al. 2008;
353 Wolff et al. 2008; Wolff et al. 2007) were considered too few in number and inconsistent to draw
354 meaningful conclusions.

355

356 Reaching clearer conclusions on “obesity” from the existing animal data was problematic.

357 Although many studies report body weight gain following developmental exposure (with

358 generally inconsistent patterns found) the workgroup emphasized that body weight is not
359 considered a good measure of obesity in rodents and only a few studies have assessed obesity
360 with the preferred metrics, e.g., fat mass, fat pad weight, and cellularity of adipocytes.
361 There is inconsistency in the *in vivo* findings that may relate to differences in experimental
362 design, e.g., diet, route of administration, and species/strain. Understanding the basis for these
363 inconsistencies was considered a research priority. The group also noted that the mechanisms of
364 BPA action are not fully understood but that it acts as more than an estrogen receptor agonist. A
365 number of *in vitro* findings suggest interactions with other receptor systems involved in
366 metabolic regulation (Wetherill et al. 2007), including anti-androgen effects at low
367 concentrations and high binding affinity for estrogen-related receptor- γ (ERR γ) (Takayanagi et
368 al. 2006).

369 **Pesticides**

370 The pesticide breakout group concluded the epidemiological, animal, and mechanistic data
371 support the biological plausibility that exposure to multiple classes of pesticides (primarily
372 insecticides) may affect risk factors for diabetes and obesity, although many significant data gaps
373 remain. Some pesticide active ingredients, insecticides in particular, impact neurotransmitter
374 and/or ion channel systems that are also involved in regulating pancreatic function, including
375 acetylcholine (e.g., organophosphate, carbamate, neo-nicotinoids), sodium channels (e.g.,
376 pyrethroids), GABA (e.g., organochlorine), catecholamine (e.g., amidine/formamidine), and
377 mitochondrial function (e.g., rotenone). This raises the possibility that these compounds might
378 affect glucose homeostasis, at least at dose levels where they are effective as pesticides (Franklin

379 and Wollheim 2004; Satin and Kinard 1998). Much less research has focused on whether
380 pesticides have activities that might affect adiposity or other risk factors for metabolic syndrome.
381
382 Case reports of hyperglycemia have been reported following poisoning incidents with a variety
383 of pesticides, perhaps best documented for organophosphates (Agency for Toxic Substances and
384 Disease Registry (ATSDR) 1997; Sungur and Guven 2001) and the formamidine insecticide
385 amitraz (Caksen et al. 2003; Elinav et al. 2005; Ertekin et al. 2002; Kennel et al. 1996; Ulukaya
386 et al. 2001; Yilmaz and Yildizdas 2003). Type 1 diabetes is a recognized complication following
387 accidental poisoning with Vacor, a rodenticide chemically similar to streptozotocin, containing
388 ~2% N-3-pyridylmethyl N'-p-nitrophenyl urea (PNU), and removed from the market in 1979
389 (Gallanosa et al. 1981; Karam et al. 1980; Miller et al. 1978; Mindel 1986; Peters et al. 1981;
390 Pont et al. 1979; Prosser and Karam 1978; Yoon 1990). With the exception of studies of
391 persistent organochlorine pesticides such as DDT/DDE or trans-nonachlor, there are very few
392 cohort studies for other pesticides and health conditions related to diabetes, metabolic syndrome,
393 or adiposity.

394

395 There is a literature reporting effects of intoxication with OP insecticides on blood glucose in
396 laboratory animals, generally finding hyperglycemia at high dose levels (Karami-Mohajeri and
397 Abdollahi 2010; Rahimi and Adbollahi 2007). Recently, the focus of investigations has shifted
398 towards studies designed to understand the consequences of developmental exposure to lower
399 doses of organophosphates and long-term health effects related to metabolic dysfunction,
400 diabetes, and obesity later in life (Adigun et al. 2010a; Adigun et al. 2010b, c; Icenogle et al.
401 2004; Lassiter et al. 2010; Lassiter et al. 2008; Levin et al. 2002; Roegge et al. 2008; Slotkin et

402 al. 2005; Slotkin et al. 2009) [reviewed in Slotkin (2010)]. The general findings are that early-life
403 exposure to otherwise subtoxic levels of OPs results in subsequently-emerging pre-diabetes,
404 abnormalities of lipid metabolism, and promotion of obesity in response to increased dietary fat.

405
406 Along with the primary literature cited in this section, the Toxicity Reference Database, or
407 ToxRefDB, was also used as a resource (<http://www.epa.gov/ncct/toxrefdb/>). The current version
408 of ToxRefDB contains data for pesticide registration purposes for 474 chemicals, primarily
409 pesticide active ingredients. These data are not available in the peer-reviewed literature.

410 ToxRefBD was queried for chemicals that caused increased body weight (or body weight gain),
411 increased blood glucose, and pancreatic effects including mass, adenomas, and non-neoplastic
412 outcomes (atrophy, congestion, hyperplasia, hypertrophy, inflammation, fatty change,
413 degeneration, cellular infiltration). Approximately 100 chemicals were identified as causing at
414 least one of these effects (<http://DNTP.niehs.nih.gov/go/36433>, see Appendix B). It is interesting
415 to note that six of the studies identified increased body weight as an outcome from treatment
416 with several organophosphates, including two separate studies for fenthion, one conducted in rats
417 and the other in mice (Table 1). Several other pesticides, sulfonylurea herbicides and imidazole
418 fungicides, identified from the ToxRefDB search belong to the same general chemical class as
419 agents either currently used to manage type 2 diabetes or being researched for their value as
420 therapeutic agents. In the majority of cases the same pesticide active ingredients identified from
421 the ToxRefBD search were also screened in ToxCast™. Preliminary analysis of these results
422 suggests that some of these chemicals may be impacting biochemical or cellular targets that have
423 not been identified in the peer-review literature but support the biological plausibility for how

424 they may exert effects on glucose homeostasis, insulin sensitivity, or adipocyte differentiation
425 and function.

426 **Utilization of Tox21 high throughput screening to identify substances of potential interest**

427 Consideration of data from the Tox21 high throughput screening initiative played a prominent
428 role in the workshop. Tox21 is a collaborative program between the EPA, NIEHS/DNTP, NIH
429 Chemical Genomics Center (NCGC), and FDA designed to research, develop, validate and
430 translate innovative chemical testing methods that characterize toxicity pathways
431 (<http://DNTP.niehs.nih.gov/go/28213>). Data from Phase I of ToxCast™, EPA’s contribution to
432 Tox21, was used to help determine the biological plausibility of reported effects as well as to
433 identify other chemicals that may interact with relevant mechanistic targets but have not been
434 assessed for effects related to diabetes or obesity. In general, the ToxCast™ data often aligned
435 with mechanistic findings in the peer-reviewed literature. The organotin fentin was identified in
436 ToxCast™ as a target for PPAR γ at a relatively low concentration
437 (<http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp>, search for “fentin”). Amitraz, a
438 formamidine insecticide, is a α 2-adrenoreceptor agonist (Chen and Hsu 1994; Hugnet et al. 1996;
439 Smith et al. 1990) and this activity was identified in ToxCast™
440 (<http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp>, search for “amitraz”).

441
442 Many of the pesticides identified from ToxRefDB™ as causing increased body weight, increased
443 blood glucose, or pancreatic effects were also screened in Phase I of ToxCast™, providing a
444 framework for considering potential mechanisms that may underlie the *in vivo* effects. In this
445 respect, it is noteworthy that many pesticides have HTS “hits” that fall outside their classic

446 pesticide mechanism of action that may be relevant to biological process of diabetes and obesity,
447 including PPAR γ . It should be noted that those chemicals, or chemical classes, with the strongest
448 associations in humans (i.e., trans-nonachlor, TCDD, DDE/DDT, PCBs, arsenic, nicotine) have
449 not yet been tested in ToxCastTM.

450
451 In brief, experts identified relevant HTS targets for several biological processes related to
452 diabetes and obesity (insulin signalling in pancreatic beta cells, islet cell function, adipocyte
453 differentiation, and feeding behaviour in *C. elegans*). Experts also suggested biological assay
454 targets that could be added to Tox21 to improve ability to identify chemicals that may perturb
455 metabolic processes. The 309 chemicals tested in Phase I of ToxCastTM, primarily pesticide
456 active ingredients, were then screened against these targets to identify a set of chemicals
457 predicted to perturb these process and others predicted to have no effect. As a follow-up activity,
458 the DNTP is initiating a targeted testing activity for a set of predicted “positives” and
459 “negatives” using more physiologically-based *in vitro* model systems.

460 **CONCLUSIONS, RESEARCH RECOMMENDATIONS, AND NEXT STEPS**

461 Overall, the workshop review of the existing literature supports the plausibility of an “obesogen”
462 hypothesis, as well as a linkage to type 2 diabetes, of varying degrees, with exposures to certain
463 chemical classes. A review of the literature indicates very little research has been directed
464 towards understanding associations of exposures to xenobiotics with type 1 diabetes. This was
465 considered a critical data gap. Many research questions remain and an important goal of this
466 workshop was to identify data gaps to stimulate focused research to move the field forward. The
467 research recommendations included suggestions for the most appropriate endpoints to evaluate in

468 human, animal and mechanistic studies of diabetes and obesity (Table 2 and Table 3).
469 Understanding more about the different phenotypes of obesity will require more sophisticated
470 measurement methods. As shown in Figure 4, the distribution of adipose tissue can vary in
471 individuals with the same BMI and waist circumference. Another series of recommendations was
472 to elucidate the role(s) of effect modifiers, confounding factors and the role of the specific
473 genetic contributions in humans and animal models used to study these diseases.

474
475 Many of the identified research gaps were not unique to the field of diabetes/obesity research.
476 The workshop noted 1) deficiencies in data on human exposures to many of the chemicals
477 examined, 2) the need for better biomarkers of exposure that may be related mechanistically to
478 the disease endpoints, 3) the need for a better understanding of the basic biology of critical cells
479 (i.e. adipocyte, beta-cell) functioning in health and disease, and 4) an appreciation of how the
480 biology that controls body weight and metabolic set points change with life stage. The workshop
481 specifically noted the need to appreciate and expect non-monotonic dose response relationships
482 for environmental influences on obesity and diabetes, and recognized the enormous complexity
483 inherent in the field. Finally, the workshop found the incorporation of high-throughput screening
484 information from the Tox21 program to be an intriguing and useful way of improving our
485 understanding of the similarities and differences in biological actions across classes of
486 chemicals, and recommended many specific targets for further assay development to further
487 enhance its utility.

488
489 NIEHS has already taken steps to address some of the research needs recognizing that some of
490 this work will best be accomplished through the DNTP and other research through the NIEHS

491 Division of Extramural Research and Training (DERT) or Division of Intramural Research
492 (DIR). Based in the results of this workshop and the data gaps noted DERT released a program
493 announcement focused on improving our understanding of the role of environmental exposures
494 in the development of obesity and diabetes (see program announcements PAR-11-170 and 171)
495 (<http://www.niehs.nih.gov/funding/grants/announcements/announcements/index.cfm>). The
496 announcement has one receipt date per year for the next three years. The DNTP is organizing
497 further *in vitro* targeted testing of some of the predictions of chemical effects from the Tox21
498 screening program, and is specifically developing an analytical method to measure organotins in
499 human blood since the essentially complete lack of exposure data to these compounds was
500 considered a critical research need.

501

502 We hope this workshop will stimulate furthering research to better understand the public health
503 impacts of environmental influences on the increasing international prevalence of diabetes,
504 obesity and metabolic syndrome. We acknowledge the dedicated efforts of the workshop
505 participants towards achieving this goal.

506 REFERENCES

- 507 [Anonymous]. 2011. Strategic Plan for NIH Obesity Research (available at
508 <http://www.obesityresearch.nih.gov/about/strategic-plan.aspx>).
509
- 510 [Anonymous]. 2010. White House Task Force on Childhood Obesity Report to the President:
511 Solving the Problem of Childhood Obesity Within a Generation (available at
512 http://www.letsmove.gov/sites/letsmove.gov/files/TaskForce_on_Childhood_Obesity_May2010_FullReport.pdf).
513
514
- 515 Adams AK, Harvey HE, Prince RJ. 2005. Association of maternal smoking with overweight at
516 age 3 y in American Indian children. *Am J Clin Nutr* 82(2): 393-398.
517
- 518 Adigun AA, Wrench N, Levin ED, Seidler FJ, Slotkin TA. 2010a. Neonatal parathion exposure
519 and interactions with a high-fat diet in adulthood: Adenylyl cyclase-mediated cell
520 signaling in heart, liver and cerebellum. *Brain Res Bull* 81(6): 605-612.
521
- 522 Adigun AA, Wrench N, Seidler FJ, Slotkin TA. 2010b. Neonatal dexamethasone treatment leads
523 to alterations in cell signaling cascades controlling hepatic and cardiac function in
524 adulthood. *Neurotoxicol Teratol* 32(2): 193-199.
525
- 526 Adigun AA, Wrench N, Seidler FJ, Slotkin TA. 2010c. Neonatal organophosphorus pesticide
527 exposure alters the developmental trajectory of cell-signaling cascades controlling
528 metabolism: differential effects of diazinon and parathion. *Environ Health Perspect*
529 118(2): 210-215.
530
- 531 Agency for Toxic Substances and Disease Registry (ATSDR). 1997. Toxicological profile for
532 Chlorpyrifos. Atlanta, GA: U.S. Department of Health and Human Services, Public
533 Health Service (available at
534 <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=495&tid=88>).
535
- 536 Aguilar MV, Martinez-Para MC, Gonzalez MJ. 1997. Effects of arsenic (V)-chromium (III)
537 interaction on plasma glucose and cholesterol levels in growing rats. *Ann Nutr Metab*
538 41(3): 189-195.
539
- 540 Al Mamun A, Lawlor DA, Alati R, O'Callaghan MJ, Williams GM, Najman JM. 2006. Does
541 maternal smoking during pregnancy have a direct effect on future offspring obesity?
542 Evidence from a prospective birth cohort study. *Am J Epidemiol* 164(4): 317-325.
543
- 544 Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, et al. 2010. Bisphenol
545 A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male
546 offspring. *Environ Health Perspect* 118(9): 1243-1250.
547

- 548 Arnold LL, Eldan M, van Gemert M, Capen CC, Cohen SM. 2003. Chronic studies evaluating
549 the carcinogenicity of monomethylarsonic acid in rats and mice. *Toxicology* 190(3): 197-
550 219.
- 551
- 552 Bergmann KE, Bergmann RL, Von Kries R, Bohm O, Richter R, Dudenhausen JW, et al. 2003.
553 Early determinants of childhood overweight and adiposity in a birth cohort study: role of
554 breast-feeding. *Int J Obes Relat Metab Disord* 27(2): 162-172.
- 555
- 556 BMJ. Best Practices Reference Material ([http://bestpractice.bmj.com/best-
557 practice/welcome.html](http://bestpractice.bmj.com/best-practice/welcome.html)).
- 558
- 559 Boas M, Frederiksen H, Feldt-Rasmussen U, Skakkebaek NE, Hegedus L, Hilsted L, et al. 2010.
560 Childhood exposure to phthalates: associations with thyroid function, insulin-like growth
561 factor I, and growth. *Environmental health perspectives* 118(10): 1458-1464.
- 562
- 563 Boerschmann H, Pfluger M, Henneberger L, Ziegler AG, Hummel S. 2010. Prevalence and
564 predictors of overweight and insulin resistance in offspring of mothers with gestational
565 diabetes mellitus. *Diabetes Care* 33(8): 1845-1849.
- 566
- 567 Boyles AL, Harris SF, Rooney AA, Thayer KA. in press. Forest Plot Viewer: a fast, flexible
568 graphing tool. *Epidemiology*.
- 569
- 570 Braun JM, Daniels JL, Poole C, Olshan AF, Hornung R, Bernert JT, et al. 2010. Prenatal
571 environmental tobacco smoke exposure and early childhood body mass index. *Paediatr
572 Perinat Epidemiol* 24(6): 524-534.
- 573
- 574 Broadmeadow A, Lee P, Ashby REA. 1984. 104 Week Combined Toxicity And Oncogenicity
575 Study In Dietary Administration To Cd Rats: Using Nf-114: Rd-84113: Report No.
576 83/Nis004/212. Un- Published Study Prepared By Life Science Research. 2826 P.
- 577
- 578 Caksen H, Odabas D, Arslan S, Akgun C, Atas B, Akbayram S, et al. 2003. Report of eight
579 children with amitraz intoxication. *Hum Exp Toxicol* 22(2): 95-97.
- 580
- 581 CDC. 2011. National Diabetes Fact Sheet, Data and Trends (available at
582 <http://apps.nccd.cdc.gov/DDTSTRS/default.aspx>).
- 583
- 584 Chan P. 1987. Ntp Technical Report On The Toxicology And Carcino- Genesis Studies Of
585 Dichlorvos (Cas No. 62-73-7) In F344/N Rats And B63F1 Mice: (Gavage Studies): Ntp
586 Tr 342. Draft Technical Report Of July, 1987 Prepared For Public Review And
587 Comment. U.
- 588
- 589 Chen A, Pennell ML, Klebanoff MA, Rogan WJ, Longnecker MP. 2006. Maternal smoking
590 during pregnancy in relation to child overweight: follow-up to age 8 years. *Int J
591 Epidemiol* 35(1): 121-130.
- 592

- 593 Chen TH, Hsu WH. 1994. Inhibition of insulin release by a formamidine pesticide amitraz and
594 its metabolites in a rat beta-cell line: an action mediated by alpha-2 adrenoceptors, a
595 GTP-binding protein and a decrease in cyclic AMP. *J Pharmacol Exp Ther* 271(3): 1240-
596 1245.
- 597
- 598 Chen Y, Ahsan H, Slavkovich V, Peltier GL, Gluskin RT, Parvez F, et al. 2010. No association
599 between arsenic exposure from drinking water and diabetes mellitus: a cross-sectional
600 study in Bangladesh. *Environmental Health Perspectives* 118(9): 1299-1305.
- 601
- 602 Cobo JM, Castineira M. 1997. Oxidative stress, mitochondrial respiration, and glycemic control:
603 clues from chronic supplementation with Cr³⁺ or As³⁺ to male Wistar rats. *Nutrition*
604 13(11-12): 965-970.
- 605
- 606 Codru N, Schymura MJ, Negoita S, Rej R, Carpenter DO. 2007. Diabetes in relation to serum
607 levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans.
608 *Environ Health Perspect* 115(10): 1442-1447.
- 609
- 610 Colosio C, Tomasini M, Cairoli S, Foa V, Minoia C, Marinovich M, et al. 1991. Occupational
611 triphenyltin acetate poisoning: a case report. *Br J Ind Med* 48(2): 136-139.
- 612
- 613 Daly I. 1996. A 24-Month Oral Toxicity/Oncogenicity Study of Malathion in the Rat via Dietary
614 Administration: Final Report: Lab Project Number: 90-3641: J-11 90-3641. Unpublished
615 study prepared by Huntingdon Life Sciences. 5666 p.
- 616
- 617 Diaz-Villasenor A, Burns AL, Hiriart M, Cebrian ME, Ostrosky-Wegman P. 2007. Arsenic-
618 induced alteration in the expression of genes related to type 2 diabetes mellitus. *Toxicol*
619 *Appl Pharmacol* 225(2): 123-133.
- 620
- 621 Diaz-Villasenor A, Burns AL, Salazar AM, Sordo M, Hiriart M, Cebrian ME, et al. 2008.
622 Arsenite reduces insulin secretion in rat pancreatic beta-cells by decreasing the calcium-
623 dependent calpain-10 proteolysis of SNAP-25. *Toxicol Appl Pharmacol* 231(3): 291-299.
- 624
- 625 Druwe IL, Vaillancourt RR. 2010. Influence of arsenate and arsenite on signal transduction
626 pathways: an update. *Arch Toxicol* 84(8): 585-596.
- 627
- 628 Dubois L, Girard M. 2006. Early determinants of overweight at 4.5 years in a population-based
629 longitudinal study. *Int J Obes (Lond)* 30(4): 610-617.
- 630
- 631 Durmus B, Kruithof CJ, Gillman MH, Willemsen SP, Hofman A, Raat H, et al. 2011. Parental
632 smoking during pregnancy, early growth, and risk of obesity in preschool children: the
633 Generation R Study. *The American journal of clinical nutrition* 94(1): 164-171.
- 634
- 635 Eiben R. 1990. MAT 7484: Study of the Chronic Toxicity and Carcinogenicity to B6C3F1
636 Mice: (Administration in the Feed for 24 Months): Lab Project Number: 100669; 19823;
637 T2024097. Unpublished study prepared by Bayer Ag. 2466 p.
- 638

- 639 Eiben R. 1989. MAT 7484: Study of the Subchronic Toxicity to Wistar Rats:(Administration in
640 the Feed for 86 Days): Lab Project Number: 99266; T1023097. Unpublished study
641 prepared by Mobay. 446 p.
642
- 643 Eiben R. 1991. Methyl parathion: Study for Chronic Toxicity and Carcinogenicity in B6C3F1
644 Mice: Administration in the Diet Over a Period of 24 Months: Lab Project Number: T
645 4027023. Unpublished study prepared by Bayer AG. 2923 p.
646
- 647 Elinav E, Shapira Y, Ofran Y, Hassin T, Ben-Dov IZ. 2005. Near-fatal amitraz intoxication: the
648 overlooked pesticide. *Basic Clin Pharmacol Toxicol* 97(3): 185-187.
649
- 650 Ertekin V, Alp H, Selimoglu MA, Karacan M. 2002. Amitraz poisoning in children:
651 retrospective analysis of 21 cases. *J Int Med Res* 30(2): 203-205.
652
- 653 Eyre H, Kahn R, Robertson RM. 2004. Preventing cancer, cardiovascular disease, and diabetes:
654 A common agenda for the American Cancer Society, the American Diabetes Association,
655 and the American Heart Association. *CA Cancer J Clin* 54(4): 190-207.
656
- 657 Feige J, Gerber A, Casals-Casas C, Yang Q, Winkler C, Bedu E, et al. 2010. The pollutant
658 diethylhexyl phthalate regulates hepatic energy metabolism via species-specific
659 PPARalpha-dependent mechanisms. *Environmental Health Perspectives* 118(2): 234-241.
660
- 661 Franklin IK, Wollheim CB. 2004. GABA in the endocrine pancreas: its putative role as an islet
662 cell paracrine-signalling molecule. *J Gen Physiol* 123(3): 185-190.
663
- 664 Fu J, Woods CG, Yehuda-Shnaidman E, Zhang Q, Wong V, Collins S, et al. 2010. Low level
665 arsenic impairs glucose-stimulated insulin secretion in pancreatic beta-cells: Involvement
666 of cellular adaptive response to oxidative stress. *Environmental Health Perspectives*
667 118(6): 864-870.
668
- 669 Gallanosa AG, Spyker DA, Curnow RT. 1981. Diabetes mellitus associated with autonomic and
670 peripheral neuropathy after Vacor rodenticide poisoning: a review. *Clin Toxicol* 18(4):
671 441-449.
672
- 673 Gillman MW, Rifas-Shiman SL, Kleinman K, Oken E, Rich-Edwards JW, Taveras EM. 2008.
674 Developmental Origins of Childhood Overweight: Potential Public Health Impact.
675 *Obesity* 16(7): 1651-1656.
676
- 677 Goodyer M. 1987. CGA-18809: Lifetime Oral (Dietary Administration) Oncogenicity Study in
678 the Mouse: Lab Project Number: 84 1214. Unpublished study prepared by Hazleton UK.
679 1472 p.
680
- 681 Gorog K, Pattenden S, Antova T, Niciu E, Rudnai P, Scholtens S, et al. 2009. Maternal Smoking
682 During Pregnancy and Childhood Obesity: Results from the CESAR Study. *Matern Child*
683 *Health J*.
684

- 685 Grun F, Blumberg B. 2006. Environmental obesogens: organotins and endocrine disruption via
686 nuclear receptor signaling. *Endocrinology* 147(6 Suppl): S50-55.
687
- 688 Grun F, Watanabe H, Zamanian Z, Maeda L, Arima K, Cubacha R, et al. 2006. Endocrine-
689 disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Mol*
690 *Endocrinol* 20(9): 2141-2155.
691
- 692 Hatch EE, Nelson JW, Qureshi MM, Weinberg J, Moore LL, Singer M, et al. 2008. Association
693 of urinary phthalate metabolite concentrations with body mass index and waist
694 circumference: a cross-sectional study of NHANES data, 1999-2002. *Environ Health* 7:
695 27.
696
- 697 Hayes R. 1989 Oncogenicity Study Of Technical Grade Tribufos (Def) With Mice: Study No.
698 86-271-01. Unpublished Study Pre- Pared By Mobay Corp. 2042 P.
699
- 700 Hill DS, Wlodarczyk BJ, Mitchell LE, Finnell RH. 2009. Arsenate-induced maternal glucose
701 intolerance and neural tube defects in a mouse model. *Toxicol Appl Pharmacol* 239(1):
702 29-36.
703
- 704 Hiromori Y, Nishikawa J, Yoshida I, Nagase H, Nakanishi T. 2009. Structure-dependent
705 activation of peroxisome proliferator-activated receptor (PPAR) gamma by organotin
706 compounds. *Chem Biol Interact* 180(2): 238-244.
707
- 708 Hugnet C, Buronrosse F, Pineau X, Cadore JL, Lorgue G, Berny PJ. 1996. Toxicity and kinetics
709 of amitraz in dogs. *Am J Vet Res* 57(10): 1506-1510.
710
- 711 Icenogle LM, Christopher NC, Blackwelder WP, Caldwell DP, Qiao D, Seidler FJ, et al. 2004.
712 Behavioral alterations in adolescent and adult rats caused by a brief subtoxic exposure to
713 chlorpyrifos during neurulation. *Neurotoxicol Teratol* 26(1): 95-101.
714
- 715 Iliadou AN, Koupil I, Villamor E, Altman D, Hultman C, Langstrom N, et al. 2010. Familial
716 factors confound the association between maternal smoking during pregnancy and young
717 adult offspring overweight. *Int J Epidemiol* 39(5): 1193-1202.
718
- 719 Inadera H, Shimomura A. 2005. Environmental chemical tributyltin augments adipocyte
720 differentiation. *Toxicol Lett* 159(3): 226-234.
721
- 722 Ino T. 2010. Maternal smoking during pregnancy and offspring obesity: meta-analysis. *Pediatr*
723 *Int* 52(1): 94-99.
724
- 725 Ino T, Shibuya T, Saito K, Ohtani T. 2011. Effects of maternal smoking during pregnancy on
726 body composition in offspring. *Pediatr Int*.
727
- 728 Itsuki-Yoneda A, Kimoto M, Tsuji H, Hiemori M, Yamashita H. 2007. Effect of a hypolipidemic
729 drug, Di (2-ethylhexyl) phthalate, on mRNA-expression associated fatty acid and acetate
730 metabolism in rat tissues. *Biosci Biotechnol Biochem* 71(2): 414-420.

- 731
732 Izquierdo-Vega JA, Soto CA, Sanchez-Pena LC, De Vizcaya-Ruiz A, Del Razo LM. 2006.
733 Diabetogenic effects and pancreatic oxidative damage in rats subchronically exposed to
734 arsenite. *Toxicol Lett* 160(2): 135-142.
735
- 736 Janesick A BB. 2011. Minireview: PPAR β as the target of obesogens. *J Steroid Biochem Mol*
737 *Biol* 0(0): 0.
738
- 739 Jorgensen ME, Borch-Johnsen K, Bjerregaard P. 2008. A cross-sectional study of the association
740 between persistent organic pollutants and glucose intolerance among Greenland Inuit.
741 *Diabetologia* 51(8): 1416-1422.
742
- 743 Kahn BB, McGraw TE. 2010. Rosiglitazone, PPAR γ , and type 2 diabetes. *New England Journal*
744 *of Medicine* 363(27): 2667-2669.
745
- 746 Kanayama T, Kobayashi N, Mamiya S, Nakanishi T, Nishikawa J. 2005. Organotin compounds
747 promote adipocyte differentiation as agonists of the peroxisome proliferator-activated
748 receptor gamma/retinoid X receptor pathway. *Mol Pharmacol* 67(3): 766-774.
749
- 750 Karam JH, Lewitt PA, Young CW, Nowlain RE, Frankel BJ, Fujiya H, et al. 1980. Insulinopenic
751 diabetes after rodenticide (Vacor) ingestion: a unique model of acquired diabetes in man.
752 *Diabetes* 29(12): 971-978.
753
- 754 Karami-Mohajeri S, Abdollahi M. 2010. Toxic effects of organophosphate, carbamate, and
755 organochlorine pesticides on cellular metabolism of lipids, proteins, and carbohydrates: A
756 comprehensive review. *Hum Exp Toxicol*.
757
- 758 Kennel O, Prince C, Garnier R. 1996. Four cases of amitraz poisoning in humans. *Vet Hum*
759 *Toxicol* 38(1): 28-30.
760
- 761 Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. 2010. Prenatal exposure to the
762 environmental obesogen tributyltin predisposes multipotent stem cells to become
763 adipocytes. *Mol Endocrinol* 24(3): 526-539.
764
- 765 Koshy G, Delpisheh A, Brabin BJ. 2011. Dose response association of pregnancy cigarette
766 smoke exposure, childhood stature, overweight and obesity. *European journal of public*
767 *health* 21(3): 286-291.
768
- 769 Koupil I, Toivanen P. 2008. Social and early-life determinants of overweight and obesity in 18-
770 year-old Swedish men. *Int J Obes (Lond)* 32(1): 73-81.
771
- 772 Kowalski R, Clemens G, Jasty Ve. 1989. A Two-generation Reproduction Study with Fenthion
773 (Baytex) in the Rat: Lab Proj- ect Nos. 99811; 1166; 8765. Unpublished study prepared
774 by Miles, Inc., Toxicology Dept. 1046 p.
775

- 776 Kuhle S, Allen AC, Veugelers PJ. 2010. Perinatal and childhood risk factors for overweight in a
777 provincial sample of Canadian Grade 5 students. *Int J Pediatr Obes* 5(1): 88-96.
778
- 779 Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL, et al. 1994. Ingested inorganic
780 arsenic and prevalence of diabetes mellitus. *Am J Epidemiol* 139(5): 484-492.
781
- 782 Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, et al. 2008.
783 Association of urinary bisphenol A concentration with medical disorders and laboratory
784 abnormalities in adults. *JAMA* 300(11): 1303-1310.
785
- 786 Lassiter TL, Ryde IT, Levin ED, Seidler FJ, Slotkin TA. 2010. Neonatal exposure to parathion
787 alters lipid metabolism in adulthood: Interactions with dietary fat intake and implications
788 for neurodevelopmental deficits. *Brain Res Bull* 81(1): 85-91.
789
- 790 Lassiter TL, Ryde IT, Mackillop EA, Brown KK, Levin ED, Seidler FJ, et al. 2008. Exposure of
791 neonatal rats to parathion elicits sex-selective reprogramming of metabolism and alters
792 the response to a high-fat diet in adulthood. *Environ Health Perspect* 116(11): 1456-1462.
793
- 794 le Maire A, Grimaldi M, Roecklin D, Dagnino S, Vivat-Hannah V, Balaguer P, et al. 2009.
795 Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors.
796 *EMBO Rep* 10(4): 367-373.
797
- 798 Lee D-H, Steffes MW, Sjodin A, Jones RS, Needham LL, Jacobs JDR. 2010. Low dose of some
799 persistent organic pollutants predicts type 2 diabetes: A nested case-control study.
800 *Environ Health Perspect* 118(9): 1235-1242.
801
- 802 Lee DH, Lee IK, Song K, Steffes M, Toscano W, Baker BA, et al. 2006. A strong dose-response
803 relation between serum concentrations of persistent organic pollutants and diabetes:
804 results from the National Health and Examination Survey 1999-2002. *Diabetes Care*
805 29(7): 1638-1644.
806
- 807 Leser K, Suberg H. 1990. E 1752: Oncogenicity Study on B6C3F1 Mice (Feeding Study for
808 Periods of up to 24 Months): Lab Project Number: 100581: 19624. Unpublished study
809 prepared by Bayer Ag. 2185 p.
810
- 811 Levin ED, Addy N, Baruah A, Elias A, Christopher NC, Seidler FJ, et al. 2002. Prenatal
812 chlorpyrifos exposure in rats causes persistent behavioral alterations. *Neurotoxicol*
813 *Teratol* 24(6): 733-741.
814
- 815 Li X, Ycaza J, Blumberg B. 2011. The environmental obesogen tributyltin chloride acts via
816 peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-
817 L1 preadipocytes. *The Journal of steroid biochemistry and molecular biology*.
818
- 819 Lina B, Til H, van Nesselrooij Jea. 1983. Six-month Oral Toxicity Study with Imazalil Base-R
820 23979 in Rats: Report No. V 83.186/220555. Unpublished study prepared by
821 Netherlands Organization for Applied Scientific Research. 234 p.

- 822
823 Luginbuehl H. 1980. Propetamphos: Chronic Feeding Study In Rats: Project No.: 279.
824 Unpublished Study Prepared By Sandoz Ltd., Basle. 2424 P.
825
- 826 Manzo L, Richelmi P, Sabbioni E, Pietra R, Bono F, Guardia L. 1981. Poisoning by triphenyltin
827 acetate. Report of two cases and determination of tin in blood and urine by neutron
828 activation analysis. *Clin Toxicol* 18(11): 1343-1353.
829
- 830 Martinelli MI, Mocchiutti NO, Bernal CA. 2010. Effect of di(2-ethylhexyl) phthalate (DEHP) on
831 lipolysis and lipoprotein lipase activities in adipose tissue of rats. *Hum Exp Toxicol*
832 29(9): 739-745.
833
- 834 Melzer D, Rice NE, Lewis C, Henley WE, Galloway TS. 2010. Association of urinary bisphenol
835 a concentration with heart disease: evidence from NHANES 2003/06. *PLoS One* 5(1):
836 e8673.
837
- 838 Miller LV, Stokes JD, Silpipat C. 1978. Diabetes mellitus and autonomic dysfunction after vacor
839 rodenticide ingestion. *Diabetes Care* 1(2): 73-76.
840
- 841 Mindel JS. 1986. N-3-pyridylmethyl-N'-p-nitrophenylurea ocular toxicity in man and an animal
842 model. *Trans Am Ophthalmol Soc* 84: 389-428.
843
- 844 Miyawaki J, Sakayama K, Kato H, Yamamoto H, Masuno H. 2007. Perinatal and postnatal
845 exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in
846 mice. *J Atheroscler Thromb* 14(5): 245-252.
847
- 848 Mizutani T, Suzuki K, Kondo N, Yamagata Z. 2007. Association of maternal lifestyles including
849 smoking during pregnancy with childhood obesity. *Obesity (Silver Spring)* 15(12): 3133-
850 3139.
851
- 852 Mobay Chemical Corp. 1983. Oncogenicity Study of Technical Di- sulfoton on Mice. Interim
853 rept. (Unpublished study received Jul 13, 1983 under 3125-58; CDL:250706-A).
854
- 855 Montgomery SM, Ekbom A. 2002. Smoking during pregnancy and diabetes mellitus in a British
856 longitudinal birth cohort. *Bmj* 324(7328): 26-27.
857
- 858 Nabi AH, Rahman MM, Islam LN. 2005. Evaluation of biochemical changes in chronic arsenic
859 poisoning among Bangladeshi patients. *Int J Environ Res Public Health* 2(3-4): 385-393.
860
- 861 Nakanishi T, Nishikawa J, Hiromori Y, Yokoyama H, Koyanagi M, Takasuga S, et al. 2005.
862 Trialkyltin compounds bind retinoid X receptor to alter human placental endocrine
863 functions. *Mol Endocrinol* 19(10): 2502-2516.
864
- 865 Naylor M, Ruecker F. 1997. Combined Chronic Toxicity/Oncogenicity Study Of Mon 37500
866 Administered In The Diet To Sprague-Dawley Rats: Lab Project Number: MI-94-118:
867 Ehl 94051: Rd 1353. Unpublished Study Prepared By Monsanto Co. 2309 P.

- 868
869 NIDDK. 2011. Diabetes Research Strategic Plan (available at
870 [http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/DiabetesPlan/Pl](http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/DiabetesPlan/PlanPosting.htm)
871 [anPosting.htm](http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/DiabetesPlan/PlanPosting.htm)).
872
- 873 NIOSH. 1976. NIOSH Criteria Document: Criteria for a Recommended Standard: Occupational
874 Exposure to Organotin Compounds (November 1976) DHHS (NIOSH) Publication No.
875 77-115 (<http://www.cdc.gov/niosh/77-115.html>).
876
- 877 Nishikawa J, Mamiya S, Kanayama T, Nishikawa T, Shiraishi F, Horiguchi T. 2004.
878 Involvement of the retinoid X receptor in the development of imposex caused by
879 organotins in gastropods. *Environ Sci Technol* 38(23): 6271-6276.
880
- 881 Ogden C, Carroll M. 2010. Prevalence of Obesity Among Children and Adolescents: United
882 States, Trends 1963-1965 Through 2007-2008. CDC-NCHS Health E-Stat (available at
883 http://www.cdc.gov/nchs/data/hestat/obesity_child_07_08/obesity_child_07_08.htm).
884
- 885 Oken E, Huh SY, Taveras EM, Rich-Edwards JW, Gillman MW. 2005. Associations of maternal
886 prenatal smoking with child adiposity and blood pressure. *Obes Res* 13(11): 2021-2028.
887
- 888 Oken E, Levitan EB, Gillman MW. 2008. Maternal smoking during pregnancy and child
889 overweight: systematic review and meta-analysis. *Int J Obes (Lond)* 32(2): 201-210.
890
- 891 Osheroff M. 1991. RH-5992: 13 Week Dietary Toxicity Study in Rats: Final Report: Lab Project
892 Number: 417-463: 89RC-101. Unpublished study prepared by Hazleton Washington, Inc.
893 775 p.
894
- 895 Padmanabhan V, Siefert K, Ransom S, Johnson T, Pinkerton J, Anderson L, et al. 2008.
896 Maternal bisphenol-A levels at delivery: a looming problem? *J Perinatol* 28(4): 258-263.
897
- 898 Paul DS, Devesa V, Hernandez-Zavala A, Adair BM, Walton FS, Drobna B, et al. 2008.
899 Environmental arsenic as a disruptor of insulin signaling. In: *Metal Ions in Biology and*
900 *Medicine: volume 10* Eds Ph Collery, I Maynard, T Theophanides, L Khassanova, T
901 Callery John Libbey Eurotext, Paris (pages 1-7).
902
- 903 Paul DS, Hernandez-Zavala A, Walton FS, Adair BM, Dedina J, Matousek T, et al. 2007.
904 Examination of the effects of arsenic on glucose homeostasis in cell culture and animal
905 studies: development of a mouse model for arsenic-induced diabetes. *Toxicol Appl*
906 *Pharmacol* 222(3): 305-314.
907
- 908 Peters KS, Tong TG, Kutz K, Benowitz NL. 1981. Diabetes mellitus and orthostatic hypotension
909 resulting from ingestion of Vacor rat poison: endocrine and autonomic function studies.
910 *West J Med* 134(1): 65-68.
911

- 912 Pettersen J, Morrissey R. 1996. (1996) 2-Year Chronic Toxicity/Oncogenicity Study With Cga-
913 277476 Technical In Rats: Final Report: Lab Project Number: F-00147. Unpublished
914 Study Prepared By Ciba-Geigy Corp., Environmental Health Center. 2806 P.
915
- 916 Pont A, Rubino JM, Bishop D, Peal R. 1979. Diabetes mellitus and neuropathy following Vacor
917 ingestion in man. *Arch Intern Med* 139(2): 185-187.
918
- 919 Power C, Atherton K, Thomas C. 2010. Maternal smoking in pregnancy, adult adiposity and
920 other risk factors for cardiovascular disease. *Atherosclerosis* 211(2): 643-648.
921
- 922 Power C, Jefferis BJ. 2002. Fetal environment and subsequent obesity: a study of maternal
923 smoking. *Int J Epidemiol* 31(2): 413-419.
924
- 925 Prosser PR, Karam JH. 1978. Diabetes mellitus following rodenticide ingestion in man. *Jama*
926 239(12): 1148-1150.
927
- 928 Rahimi R, Adbollahi M. 2007. A review on the mechanisms involved in hyperglycemia induced
929 by organophosphorus pesticides. *Pesticide Biochemistry and Physiology* 88(115-121).
930
- 931 Rahman M, Tondel M, Ahmad SA, Axelson O. 1998. Diabetes mellitus associated with arsenic
932 exposure in Bangladesh. *Am J Epidemiol* 148(2): 198-203.
933
- 934 Rahman M, Tondel M, Chowdhury IA, Axelson O. 1999. Relations between exposure to arsenic,
935 skin lesions, and glucosuria. *Occup Environ Med* 56(4): 277-281.
936
- 937 Raum E, Kupper-Nybelen J, Lamerz A, Hebebrand J, Herpertz-Dahlmann B, Brenner H. 2011.
938 Tobacco Smoke Exposure Before, During, and After Pregnancy and Risk of Overweight
939 at Age 6. Obesity (Silver Spring, Md).
940
- 941 Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. 2005. Early life risk
942 factors for obesity in childhood: cohort study. *Bmj* 330(7504): 1357.
943
- 944 Rignell-Hydbom A, Lidfeldt J, Kiviranta H, Rantakokko P, Samsioe G, Agardh CD, et al. 2009.
945 Exposure to p,p'-DDE: a risk factor for type 2 diabetes. *PLoS One* 4(10): e7503.
946
- 947 Rignell-Hydbom A, Rylander L, Hagmar L. 2007. Exposure to persistent organochlorine
948 pollutants and type 2 diabetes mellitus. *Hum Exp Toxicol* 26(5): 447-452.
949
- 950 Roegge CS, Timofeeva OA, Seidler FJ, Slotkin TA, Levin ED. 2008. Developmental diazinon
951 neurotoxicity in rats: later effects on emotional response. *Brain Res Bull* 75(1): 166-172.
952
- 953 Rooney BL, Mathiason MA, Schauburger CW. 2010. Predictors of Obesity in Childhood,
954 Adolescence, and Adulthood in a Birth Cohort. *Maternal and child health journal*.
955

- 956 Ryan KK, Haller AM, Sorrell JE, Woods SC, Jandacek RJ, Seeley RJ. 2010. Perinatal exposure
957 to bisphenol-a and the development of metabolic syndrome in CD-1 mice. *Endocrinology*
958 151(6): 2603-2612.
- 959
- 960 Rylander L, Rignell-Hydbom A, Hagmar L. 2005. A cross-sectional study of the association
961 between persistent organochlorine pollutants and diabetes. *Environ Health* 4: 28.
962
- 963 Sakurai T, Miyazawa S, Hashimoto T. 1978. Effects of di-(2-ethylhexyl)phthalate administration
964 on carbohydrate and fatty acid metabolism in rat liver. *J Biochem* 83(1): 313-320.
965
- 966 Salsberry PJ, Reagan PB. 2005. Dynamics of early childhood overweight. *Pediatrics* 116(6):
967 1329-1338.
968
- 969 Salsberry PJ, Reagan PB. 2007. Taking the long view: the prenatal environment and early
970 adolescent overweight. *Res Nurs Health* 30(3): 297-307.
971
- 972 Satin LS, Kinard TA. 1998. Neurotransmitters and their receptors in the islets of Langerhans of
973 the pancreas: what messages do acetylcholine, glutamate, and GABA transmit?
974 *Endocrine* 8(3): 213-223.
975
- 976 Sharma AJ, Cogswell ME, Li R. 2008. Dose-response associations between maternal smoking
977 during pregnancy and subsequent childhood obesity: effect modification by maternal
978 race/ethnicity in a low-income US cohort. *Am J Epidemiol* 168(9): 995-1007.
979
- 980 Slotkin TA. 2010. Does Early-Life Exposure to Organophosphate Insecticides Lead to
981 Prediabetes and Obesity? *Reproductive toxicology* (Elmsford, NY).
982
- 983 Slotkin TA, Brown KK, Seidler FJ. 2005. Developmental exposure of rats to chlorpyrifos elicits
984 sex-selective hyperlipidemia and hyperinsulinemia in adulthood. *Environ Health Perspect*
985 113(10): 1291-1294.
986
- 987 Slotkin TA, Lassiter TL, Ryde IT, Wrench N, Levin ED, Seidler FJ. 2009. Consumption of a
988 high-fat diet in adulthood ameliorates the effects of neonatal parathion exposure on
989 acetylcholine systems in rat brain regions. *Environ Health Perspect* 117(6): 916-922.
990
- 991 Smith BE, Hsu WH, Yang PC. 1990. Amitraz-induced glucose intolerance in rats: antagonism by
992 yohimbine but not by prazosin. *Arch Toxicol* 64(8): 680-683.
993
- 994 Somm E, Schwitzgebel VM, Toulotte A, Cederroth CR, Combescure C, Nef S, et al. 2009.
995 Perinatal exposure to bisphenol a alters early adipogenesis in the rat. *Environ Health*
996 *Perspect* 117(10): 1549-1555.
997
- 998 Squire R. 1988. An Evaluation Of Vascular Proliferative Lesions In Male Wistar Rats From
999 Project 70C0326/8241: Chronic Toxicity And Oncogenicity: Dimethoate. Unpublished
1000 Study Prepared By Robert A. Squire Associates, Inc. 41 P.
1001

- 1002 Stahlhut RW, van Wijngaarden E, Dye TD, Cook S, Swan SH. 2007. Concentrations of urinary
1003 phthalate metabolites are associated with increased waist circumference and insulin
1004 resistance in adult U.S. males. *Environ Health Perspect* 115(6): 876-882.
1005
- 1006 Sungur M, Guven M. 2001. Intensive care management of organophosphate insecticide
1007 poisoning. *Crit Care* 5(4): 211-215.
1008
- 1009 Suzuki K, Ando D, Sato M, Tanaka T, Kondo N, Yamagata Z. 2009. The association between
1010 maternal smoking during pregnancy and childhood obesity persists to the age of 9-10
1011 years. *J Epidemiol* 19(3): 136-142.
1012
- 1013 Tai C. 1985. CGA-131036 Technical: 90-day Oral Toxicity Study in Rats: Lab Study No. 85021.
1014 Unpublished study prepared by Ciba-Geigy Ltd. 365 p.
1015
- 1016 Takayanagi S, Tokunaga T, Liu X, Okada H, Matsushima A, Shimohigashi Y. 2006. Endocrine
1017 disruptor bisphenol A strongly binds to human estrogen-related receptor gamma
1018 (ERRgamma) with high constitutive activity. *Toxicol Lett* 167(2): 95-105.
1019
- 1020 Tobia A. 1987. Combined Chronic Toxicity/Oncogenicity Study with INL-5300: Long-term
1021 Feeding Study in Rats: Haskel Laboratory Re- port No. 61-87: [includes Supplementary
1022 Report, prepared by F. O'Neal]. Unpublished study prepared by Haskell Laboratory f.
1023
- 1024 Tollestrup K, Frost FJ, Harter LC, McMillan GP. 2003. Mortality among children residing near
1025 the American Smelting and Refining Company (ASARCO) copper smelter in Ruston,
1026 Washington. *Arch Environ Health* 58(11): 683-691.
1027
- 1028 Tome FS, Cardoso VC, Barbieri MA, Silva AA, Simoes VM, Garcia CA, et al. 2007. Are birth
1029 weight and maternal smoking during pregnancy associated with malnutrition and excess
1030 weight among school age children? *Braz J Med Biol Res* 40(9): 1221-1230.
1031
- 1032 Toschke AM, Koletzko B, Slikker W, Jr., Hermann M, von Kries R. 2002. Childhood obesity is
1033 associated with maternal smoking in pregnancy. *Eur J Pediatr* 161(8): 445-448.
1034
- 1035 Toschke AM, Montgomery SM, Pfeiffer U, von Kries R. 2003. Early Intrauterine Exposure to
1036 Tobacco-inhaled Products and Obesity. *Am J Epidemiol* 158(11): 1068-1074.
1037
- 1038 Toschke AM, Ruckinger S, Bohler E, Von Kries R. 2007. Adjusted population attributable
1039 fractions and preventable potential of risk factors for childhood obesity. *Public Health*
1040 *Nutr* 10(9): 902-906.
1041
- 1042 Tsai SM, Wang TN, Ko YC. 1999. Mortality for certain diseases in areas with high levels of
1043 arsenic in drinking water. *Arch Environ Health* 54(3): 186-193.
1044
- 1045 Tseng CH. 2004. The potential biological mechanisms of arsenic-induced diabetes mellitus.
1046 *Toxicol Appl Pharmacol* 197(2): 67-83.
1047

- 1048 Tseng CH, Tai TY, Chong CK, Tseng CP, Lai MS, Lin BJ, et al. 2000. Long-term arsenic
1049 exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in
1050 arseniasis-hyperendemic villages in Taiwan. *Environ Health Perspect* 108(9): 847-851.
1051
- 1052 Turyk M, Anderson H, Knobeloch L, Imm P, Persky V. 2009a. Organochlorine exposure and
1053 incidence of diabetes in a cohort of Great Lakes sport fish consumers. *Environ Health*
1054 *Perspect* 117(7): 1076-1082.
1055
- 1056 Turyk M, Anderson HA, Knobeloch L, Imm P, Persky VW. 2009b. Prevalence of diabetes and
1057 body burdens of polychlorinated biphenyls, polybrominated diphenyl ethers, and p,p'-
1058 diphenyldichloroethene in Great Lakes sport fish consumers. *Chemosphere* 75(5): 674-
1059 679.
1060
- 1061 Uemura H, Arisawa K, Hiyoshi M, Satoh H, Sumiyoshi Y, Morinaga K, et al. 2008. Associations
1062 of environmental exposure to dioxins with prevalent diabetes among general inhabitants
1063 in Japan. *Environ Res* 108(1): 63-68.
1064
- 1065 Ukropec J, Radikova Z, Huckova M, Koska J, Kocan A, Sebokova E, et al. 2010. High
1066 prevalence of prediabetes and diabetes in a population exposed to high levels of an
1067 organochlorine cocktail. *Diabetologia*.
1068
- 1069 Ulukaya S, Demirag K, Moral AR. 2001. Acute amitraz intoxication in human. *Intensive Care*
1070 *Med* 27(5): 930-933.
1071
- 1072 Vasiliu O, Cameron L, Gardiner J, Deguire P, Karmaus W. 2006. Polybrominated biphenyls,
1073 polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus.
1074 *Epidemiology* 17(4): 352-359.
1075
- 1076 Verstraeten A. 1993. Carcinogenicity Study in Swiss Mice: Imazalil Base: Final Report:
1077 Nonclinical Laboratory Study: Lab Project Number: 2194: R 23979. Unpublished study
1078 prepared by Janssen Research Foundation. 1004 p.
1079
- 1080 von Kries R, Bolte G, Baghi L, Toschke AM, for the GMESG. 2008. Parental smoking and
1081 childhood obesity--is maternal smoking in pregnancy the critical exposure? *Int J*
1082 *Epidemiol* 37(1): 210-216.
1083
- 1084 von Kries R, Toschke AM, Koletzko B, Slikker W, Jr. 2002. Maternal Smoking during
1085 Pregnancy and Childhood Obesity. *Am J Epidemiol* 156(10): 954-961.
1086
- 1087 Wang JP, Wang SL, Lin Q, Zhang L, Huang D, Ng JC. 2009. Association of arsenic and kidney
1088 dysfunction in people with diabetes and validation of its effects in rats. *Environ Int* 35(3):
1089 507-511.
1090
- 1091 Wang SL, Chiou JM, Chen CJ, Tseng CH, Chou WL, Wang CC, et al. 2003. Prevalence of non-
1092 insulin-dependent diabetes mellitus and related vascular diseases in southwestern

- 1093 arseniasis-endemic and nonendemic areas in Taiwan. Environ Health Perspect 111(2):
1094 155-159.
- 1095
- 1096 Wang SL, Tsai PC, Yang CY, Leon Guo Y. 2008. Increased risk of diabetes and polychlorinated
1097 biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care
1098 31(8): 1574-1579.
- 1099
- 1100 Wang YX. 2010. PPARs: diverse regulators in energy metabolism and metabolic diseases. Cell
1101 Res 20(2): 124-137.
- 1102
- 1103 Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, et al. 2007.
1104 *In vitro* molecular mechanisms of bisphenol A action. Reproductive toxicology
1105 (Elmsford, NY 24(2): 178-198.
- 1106
- 1107 Whitaker RC. 2004. Predicting Preschooler Obesity at Birth: The Role of Maternal Obesity in
1108 Early Pregnancy. Pediatrics 114(1): e29-36.
- 1109
- 1110 WHO. 2011. Obesity and overweight (updated March 2011 and available at
1111 <http://www.who.int/mediacentre/factsheets/fs311/en/index.html>).
- 1112
- 1113 Widerøe M, Torstein V, Jacobsen G, Bakketeig L. 2003. Does maternal smoking during
1114 pregnancy cause childhood overweight? Paediatr Perinat Epidemiol 17(2): 171-179.
- 1115
- 1116 Wolff M, Engel S, Berkowitz G, Ye X SM, Zhu C, Wetmur J, et al. 2008. Prenatal phenol and
1117 phthalate exposures and birth outcomes Environ Health Perspect 116(8): 1092-1097.
- 1118
- 1119 Wolff MS, Teitelbaum SL, Windham G, Pinney SM, Britton JA, Chelimo C, et al. 2007. Pilot
1120 study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. Environ
1121 Health Perspect 115(1): 116-121.
- 1122
- 1123 Yilmaz HL, Yildizdas DR. 2003. Amitraz poisoning, an emerging problem: epidemiology,
1124 clinical features, management, and preventive strategies. Arch Dis Child 88(2): 130-134.
- 1125
- 1126 Yoon JW. 1990. The role of viruses and environmental factors in the induction of diabetes. Curr
1127 Top Microbiol Immunol 164: 95-123.
- 1128
- 1129
- 1130

1130 **FIGURE AND TABLE LEGENDS**

1131 **Figure 1.** Association between maternal smoking and overweight/obesity in offspring.

1132 Abbreviations: Amer. Ind – American Indian; ALSPAC – Avon Longitudinal Study of Parents
 1133 and Children; adjOR – adjusted odds ratio; BBC – British Birth Cohort; BMI – body mass index;
 1134 CESAR – Central European Study on Air Pollution and Respiratory Health; CLASS – Children’s
 1135 Lifestyle and School Performance study; CPP – Collaborative Perinatal Project, GDM –
 1136 gestational diabetes mellitus, Gen R – Generation R study; NCDS – National Child
 1137 Development Study; NLSY – National Longitudinal Survey of Youth, PedNSS – Pediatric
 1138 Nutrition Surveillance System, WIC – Women, Infants, and Children program, RR– relative risk;
 1139 wt. – weight; ref. – referent group

1140 *Risk estimates for bracketed statistics, i.e., [crudeRR] calculated based on data presented in the
 1141 paper using an open source epidemiology statistics programs, OpenEpi
 1142 (<http://www.openepi.com/menu/openEpiMenu.htm>)

1143 **Figure 2.** Association between arsenic and diabetes in areas of relatively high exposures (>150
 1144 ppm drinking water).

1145 Abbreviations: As – arsenic; adjOR – adjusted odds ratio; CEI – cumulative exposure index; CS
 1146 – cross sectional; HEALS – Health Effects of Arsenic Longitudinal Study; OGTT – oral glucose
 1147 tolerance test; PR – prevalence ratio; Pros – prospective; Retro – retrospective; RR – relative
 1148 risk; SMR – standardized mortality ratio

1149 *Risk estimates for bracketed statistics, i.e., [SMR] and [RR] were estimated by Navas-Acien et
 1150 al. (2006)

1151

1152 **Figure 3.** Association between PCBs and diabetes

1153 Abbreviations: adjOR – adjusted odds ratio; CARDIA – Coronary Artery Risk Development in
1154 Young Adults; CC – case control; CS – cross sectional; NHANES – National Health and
1155 Nutrition Examination Survey; PBB – polybrominated biphenyl; Pros – prospective; WHILA –
1156 Women’s Health in the Lund Area

1157 **Figure 4.** Imaging different types of obesity: Two subjects with the same BMI (32.0) and waist
1158 circumference (112 cm).

1159 **Table 1.** Selected results from ToxRefDB search for chemicals that caused increased body
1160 weight (or body weight gain), increased glucose, or pancreatic effects

1161 The complete list can be found at

1162 [http://ntp.niehs.nih.gov/ntp/ohat/diabetesobesity/Wkshp/PesticidesDraftLiteratureReviewV3form](http://ntp.niehs.nih.gov/ntp/ohat/diabetesobesity/Wkshp/PesticidesDraftLiteratureReviewV3formatted.pdf)
1163 [atted.pdf](http://ntp.niehs.nih.gov/ntp/ohat/diabetesobesity/Wkshp/PesticidesDraftLiteratureReviewV3formatted.pdf) (see Table 9).

1164 **Table 2.** Research recommendations for health outcome assessment measures

1165 **Table 3.** Diagnostic criteria, signs/symptoms, and risk factors for diabetes and obesity (BMJ)

1166