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Review

A systematic review and meta-analysis of environmental contaminant exposure impacts on weight loss and glucose regulation during calorie-restricted diets in preclinical studies: Persistent organic pollutants may impede glycemic control

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ABSTRACT

Epidemiological evidence links chemical exposure with type 2 diabetes (T2DM) risk and prevalence. Chemical exposure may therefore also limit success of weight loss or restoration of glycemic control during calorie restricted diets. Few human studies examine this hypothesis. This systematic review and clustered meta-analysis examines preclinical evidence that exposure to anthropogenic environmental contaminants impedes weight loss and resumption of glycemic control during calorie restriction. Of five eligible papers from 212 unique citations, four used C57BL/6 mice and one used Sprague Dawley rats. In four the animals received high fat diets to induce obesity and impaired glycemic control. All examined persistent organic pollutants (POPs). Polychlorinated biphenyl (PCB) 77 exposure did not affect final mass (standardised mean difference (SMD) = -0.35 [-1.09, 0.39]; n = 5 (experiments); n = 3 (papers)), or response to insulin in insulin tolerance tests (SMD = -1.54 [-3.25, 0.16] n = 3 (experiments); n = 2 (papers)), but impaired glucose control in glucose tolerance tests (SMD = -1.30 [-1.96, -0.63]; n = 6 (experiments); n = 3 (papers)). The impaired glycemic control following perfluoro-octane sulphonic acid (PFOS) exposure and enhanced mass loss following dichlorodiphenyltrichloroethane (DDT) exposure have not been replicated. Animal studies thus suggest some chemical groups, especially PCB and PFOS, could

Abbreviations: AhR, Aryl hydrocarbon receptor; AhR +/+, Mice wild type for AhR; AhR -/-, Mice knockout for AhR; AhR^{ADQ}, Adipocyte-specific AhR deficient mice produce using cre-lox technology; AhR^{fln}, Sham AhR adipocyte specific knock down mice; ARRIVE, Animal Research: Reporting of In Vivo Experiments; ATBC, Acetyl tributyl citrate (ATBC); AUC, Area under the curve; BMI, Body mass index; BPA, Bisphenol A; C57BL/6, C57 black 6 mouse – a commonly used inbred laboratory mouse strain; CB77, Chlorobiphenyl 77; 3, 3',4,4'-Tetrachlorobiphenyl; CB126, Chlorobiphenyl 126; 3, 3',4,4',5-Pentachlorobiphenyl; CB209, Chlorobiphenyl 209; 4-Chloro-1, 1'-biphenyl; DDE, Dichlorodiphenyldichloroethylene; DDT, Dichlorodiphenyltrichloroethane; DEHP, Di(2-ethylhexyl) phthalate; DINCH, 1,2-Cyclohexane dicarboxylic acid diisononyl ester; DL-PCBs, Dioxin-like PCBs; DOI, Digital object identifier; F, Female; GC-MS/MS, Gas chromatography coupled to tandem mass spectrometry; GTT, Glucose tolerance test; h, hours; HbA1c, Glycated hemoglobin A1c; HCB, Hexachlorobenzene; HFD, High fat diet; HOMA, Homeostatic model assessment; HOMA-β, Homeostatic model assessment for β-cell function; HOMA-IR, Homeostatic model assessment for insulin resistance; IGT, Impaired glucose tolerance; ISO, International Organization for Standardization; ITT, Insulin tolerance test; K, Number of individual studies used in a meta analysis; LFD, Low fat diet; M, Male; MeSH, Medical subject headings; MINCH, cyclohexane-1,2-dicarboxylic monoisononyl ester; mo, months; n, Sample size; NASH, Non-alcoholic steatohepatitis; NHS, National Health Service (UK); NOAEL, No observed adverse effect level; OCPs, Organochlorine pesticides, a group of chlorinated POPs; OSF, Open Science Framework; PAH, Poly aromatic hydrocarbons; PBDEs, Polybrominated diphenyl ethers, a group of brominated POPs; PCBs, Polychlorinated biphenyls, a group of chlorinated POPs; PECO, Population Exposure Context/ Comparison Outcome; PFAS, Per- and polyfluorinated Substances; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctanesulfonic acid; PM_{2.5}, Particulate matter of 2.5 μm or less; PM₁₀, Particulate matter of 10 μm or less; POPs, Persistent organic pollutants; PREPARE, Planning Research and Experimental Procedures on Animals: Recommendations for Excellence; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RoB, Risk of Bias; sd, Standard deviation; SMD, Standard mean difference; SYRCLC, SYStematic Review Centre for Laboratory animal Experimentation; T2DM, Type 2 diabetes mellitus; TASH, Toxin-induced steatohepatitis; TCDD, 2,3,7,8-Tetrachlorodibenzo-p-dioxin; [tiab], Present in title and abstract; TOTM, tris (2-ethylhexyl) trimellitate; WoS, Web of Science.

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impair glucose control management during calorie restriction, similar to conclusions from limited existing clinical studies. We discuss the research that is urgently required to inform weight management services that are now the mainstay prevention initiative for T2DM.

1. Introduction

The production and release of chemicals into the environment is outstripping the capacity to monitor and regulate them [1]. Humans are thus unintentionally, but continuously, exposed to an overwhelming and increasing array of chemical pollutants in daily life through food, water, air and contact with everyday items [2]. Chemical pollutants linked to a range of human health impacts include legacy contaminants, such as polychlorinated biphenyls (PCBs), polybrominated di-ethyl ethers (PBDEs), organochlorine pesticides (OCPs), ‘forever chemicals’, such as per and poly-fluorinated compounds (PFAS) and heavy metals that are persistent in the environment and often bio-accumulative. Ubiquitous and pseudo-persistent pollutants, such as those associated with plastic production, including bisphenols and phthalates, widely used non-bio-accumulative pesticides, and air pollutants are also of major concern for human health.

Growing epidemiological evidence shows compelling links between environmental exposures and the incidence and prevalence of both type 2 diabetes (T2DM) and obesity for an expanding suite of chemical classes [3–12]. Experimental evidence in preclinical studies supports many of these associations and provides plausible mechanistic detail [13–18]. Over a decade ago expert groups recommended more research on the association between chemical exposure and the incidence and prevalence of T2DM and obesity, given the alarming parallel increases in pervasive human exposure to chemical pollution and metabolic disease [19].

Significant and sustained diet-controlled weight loss is one of the most effective ways to manage T2DM and other obesity related conditions without surgery [20–25]. Successful weight loss is difficult to achieve and maintain, for multiple reasons, many of which are understood (eg lifestyle or endocrine). Less well understood is the fact that glycemic control is not achieved in 10–15 % of cases despite clinically relevant weight loss [24–26]. The reasons for lack of success in weight loss and the decoupling of weight loss from resumption of glycemic control are not understood, and cannot be fully explained by lack of motivation, or genotype-diet interactions [27,28]. Since intentional weight loss is the first line of management of T2DM, and widely being supported by health systems around the globe, it is important to understand the reasons for poor success rates more fully. One possible cause is an impact of highly prevalent environmental chemicals on the response to these interventions, given their known associations with T2DM prevalence.

Despite evidence of causal links with aetiology, the effect of chemical exposure on the effectiveness of T2DM management or diet interventions is rarely addressed in clinical studies. Animal studies may complement evidence from clinical research and provide important additional translational and mechanistic information, particularly because their food intake can be much more tightly controlled than that of humans enlisted into clinical trials. Animal models can allow investigation of events during early development, assess a wider range of outcomes, control exposure and diet to a greater extent, and minimise a range of confounds compared to human trials [29]. Shorter lifespan also makes chronic exposures feasible. Greater understanding of the role and extent of chemical exposure in effectiveness of diet-induced weight loss interventions may thus be facilitated by examining evidence from *in vivo* animal studies.

In this review we systematically searched and synthesised the literature that examines the effect of environmental pollutant exposure on intentional, diet-induced weight loss in animal studies, to 1. map the scope and nature of preclinical evidence that environmental pollutants

impede weight management and subsequent glycemic control; 2. identify chemicals that are most commonly examined, and most strongly associated with impaired weight loss; 3. evaluate the strength of available preclinical evidence that chemical exposure can impair weight loss and associated metabolic parameters; 4. establish whether the preclinical data support the sparse clinical findings and 5. assess the value of the animal studies for their clinical implications for T2DM management and prevention in humans. This information will help identify chemicals of greatest concern and may indicate clinically important outcomes to assess for targeted human studies. A weight of evidence approach will help determine if chemical exposure can impede weight loss and thus inform whether screening for specific chemical classes in patients attempting to lose weight may ultimately be warranted to improve and maximise effectiveness of obesity and T2DM management.

2. Methods

Study selection, screening and data extraction followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [30]. The protocol is registered in PROSPERO (CRD42022339993). We focus here on the animal studies identified.

2.1. Search

We searched PubMed, Web of Knowledge, and Scopus for keywords in the title and/or abstract (Table 1) [31] using the population, exposure, context, outcome (PECO) framework [32]. We considered all animal subjects of any species, strain or genetic background undergoing intentional, diet-induced weight loss, comprising healthy individuals and those with genetic or high fat diet-induced obesity.

We excluded papers in which weight loss occurred due to bariatric surgery, or unintentionally from disease or during a natural weight loss period, such as extended fasting in wildlife, and those that involved diets that were not intended to cause weight loss, such as replacement of calories with other macronutrients, or studies in which a food restriction phase or group was able to maintain or increase body weight, since these diets were clearly calorifically adequate. We excluded those studies investigating chemical induced weight loss by specifically targeting appetite and in which the exposed group was therefore compared to a food-intake matched group intended to induce equivalent weight loss to the chemical. This study design was intended to disentangle loss of appetite or mass loss caused by chemical exposure from fasting alone. In these cases, weight loss in the exposed group was not intentional and the control weight loss group did not receive the chemical of interest.

We considered all studies that included any experimental exposure to a chemical of environmental concern that has been identified in at least one epidemiological study as a potential risk factor in development of T2DM or obesity, metabolic syndrome, insulin insensitivity, non-alcoholic steatohepatitis (NASH), or toxin-induced steatohepatitis (TASH: [33]).

There were no limits on the context of the studies that were included, provided they were conducted in animals. There was no limit placed on the diet duration or nature of the dietary intervention, so long as it was intended to cause weight loss.

The main outcome of interest was rate or magnitude of weight loss or fat reduction, including changes in body mass, percentage fat, and other metrics associated with weight reduction that relate to a fall in the size of adipose reserves, such as an absolute or relative reduction in adipose cell size in different depots. Secondary outcomes included measures of glycemic control (fasting glucose, fasting insulin, glycated hemoglobin

Table 1
Search strategy and terms for the three databases used in this review.

Operator	Concept	Search terms
Pubmed	Dietary induced, intentional weight loss in people or animals	("Weight Reduction Programs"[Mesh] OR "Diet, Reducing"[Mesh] OR "Diet, Fat-Restricted" [Mesh] OR "Diet, Carbohydrate-Restricted"[Mesh] OR intentional [tiab] OR "dietary intervention" [tiab] OR "caloric restriction" [tiab] OR "calorie restriction" [tiab] OR "meal replacement" [tiab] OR diet n1 restrict* [tiab])
AND	Chemical exposure	("Hydrocarbons, Chlorinated"[Mesh] OR "Hydrocarbons, Brominated"[Mesh] OR "Hydrocarbons, Fluorinated"[Mesh] OR "Hydrocarbons, Halogenated"[Mesh] OR "Dioxins and Dioxin-like Compounds"[Mesh] OR "Halogenated Diphenyl Ethers"[Mesh] OR "Persistent Organic Pollutants"[Mesh] OR "Pesticides"[Mesh] OR "Dibutyl Phthalate"[Mesh] OR "Diethylhexyl Phthalate"[Mesh] OR "Organotin Compounds"[Mesh] OR "Parabens"[Mesh] OR "Neonicotinoids"[Mesh] OR "polychlorinated biphenyl*" [tiab] OR "persistent organic pollutant*" [tiab] OR Aroclor [tiab] OR dioxin* [tiab] OR TCDD [tiab] OR "polybrominated diphenyl ether*" [tiab] OR "polybrominated diethyl ether*" [tiab] OR PBDE* [tiab] OR organochlorine* [tiab] OR DDT [tiab] OR dichlorodiphenyltrichloroethane [tiab] OR "dichlorodiphenyl trichloroethane" [tiab] OR DDE [tiab] OR dichlorodiphenyldichloroethylene [tiab] OR "dichlorodiphenyl dichloroethylene" [tiab] OR heptachlor [tiab] OR nonachlor [tiab] OR HCB [tiab] OR hexachlorobenzene [tiab] OR pyrethroid [tiab] OR "phenoxybenzoic acid " [tiab] OR aldrin [tiab] OR chlordan* [tiab] OR dichlorvos [tiab] OR mevinphos [tiab] OR trichlorfon [tiab] OR alachlor [tiab] OR cyanazine [tiab] OR dieldrin [tiab] OR endrin [tiab] OR hexachlorocyclohexane [tiab] OR endosulfan [tiab] OR PFAS [tiab] OR PFOS [tiab] OR "perfluorooctane sulfonic acid" [tiab] OR PFOA [tiab] OR "perfluorooctanoic acid" [tiab] OR phthalate* [tiab] OR MEHP [tiab] OR DEHP [tiab] OR bisphenol* [tiab] OR BPA [tiab] OR arsenic [tiab] OR cadmium [tiab] OR mercury [tiab] OR tributyltin [tiab] OR organotin [tiab] OR triphenyltin [tiab] OR triclocarban [tiab] OR triclosan [tiab] OR paraben* [tiab] OR carbamate [tiab] OR aldicarb [tiab] OR carbaryl [tiab] OR furan* [tiab] OR neonicotinoid* [tiab] OR imidacloprid [tiab] OR acetamiprid [tiab] OR dinotefuran [tiab] OR thiamethoxam [tiab] OR clothianidin [tiab] OR fipronil [tiab] OR PM2.5 [tiab] OR PM10 [tiab] OR particulate [tiab] OR ozone [tiab] OR "nitrogen oxide"[tiab] OR "nitrogen dioxide" [tiab] OR "sulphur dioxide" [tiab] OR "sulfur dioxide"[tiab] OR "carbon monoxide" [tiab] OR "black carbon" [tiab] OR "polyaromatic hydrocarbon" [tiab] OR "PAH"[tiab])
AND	Weight loss outcomes	("weight loss" [tiab] OR "mass loss" [tiab] OR "weight reduc*" [tiab] OR "mass reduc*" [tiab] OR weight n1 reduc* [tiab] OR "waist circumference" [tiab] OR "waist-hip ratio" [tiab] OR "waist to hip ratio" [tiab] OR BMI [tiab] OR "body mass index" [tiab] OR "body fat" [tiab] OR "adiposity" [tiab] OR "fat reduc*" [tiab] OR "fat loss"[tiab])
NOT	Bariatric surgery	("bariatric surgery"[Mesh] OR "bariatric surgery" [tiab] OR "bariatric procedur*" [tiab] OR "Roux-en-Y " [tiab] OR "gastric band*" [tiab] OR "sleeve gastrectomy" [tiab] OR "gastric bypass" [tiab] OR "gastroplasty" [tiab] OR "jejunoileal bypass" [tiab] OR "stomach stapl*" [tiab])
Web of Science	Dietary induced, intentional weight loss in people or animals	TS= ("Weight Reduction Program*" OR "Reducing Diet" OR "Fat-Restricted Diet" OR "Carbohydrate-Restricted Diet" OR intentional OR "dietary intervention" OR "caloric restriction" OR "calorie restriction" OR "meal replacement" OR diet near/1 restrict*)
AND	Chemical exposure	TS = ("Chlorinated Hydrocarbon*" OR "Brominated Hydrocarbon*" OR "Fluorinated Hydrocarbon*" OR "Halogenated Hydrocarbon*" OR Dioxin OR "Dioxin-like" OR "Halogenated Diphenyl Ethers" OR "Persistent Organic Pollutant*" OR "Pesticide" OR "Dibutyl Phthalate" OR "Diethylhexyl Phthalate" OR "Organotin Compound" OR "Parabens" OR "polychlorinated biphenyl*" OR "polyaromatic hydrocarbon*" OR Aroclor OR TCDD OR "polybrominated diphenyl ether*" OR "polybrominated diethyl ether*" OR PBDE* OR organochlorine* OR DDT OR dichlorodiphenyltrichloroethane OR "dichlorodiphenyl trichloroethane" OR DDE OR dichlorodiphenyldichloroethylene OR "dichlorodiphenyl dichloroethylene" OR heptachlor OR nonachlor OR HCB OR hexachlorobenzene OR pyrethroid OR "phenoxybenzoic acid" OR aldrin OR chlordan* OR dichlorvos OR mevinphos OR trichlorfon OR alachlor OR cyanazine OR dieldrin OR endrin OR hexachlorocyclohexane OR lindane OR endosulfan OR PFAS OR PFOS OR "perfluorooctane sulfonic acid" OR PFOA OR "perfluorooctanoic acid" OR phthalate* OR MEHP OR DEHP OR bisphenol* OR BPA OR arsenic OR cadmium OR mercury OR tributyltin OR organotin OR triphenyltin OR triclocarban OR triclosan OR paraben* OR carbamate OR carbaryl OR furan* OR neonicotinoid* OR imidacloprid OR acetamiprid OR dinotefuran OR thiamethoxam OR clothianidin OR fipronil OR PM2.5 OR PM10 OR particulate OR ozone OR "nitrogen oxide" OR "nitrogen dioxide" OR "sulphur dioxide" OR "sulfur dioxide" OR "carbon monoxide" OR "black carbon" OR "polyaromatic hydrocarbon" OR "PAH")
AND	Weight loss outcomes	TS= ("weight loss" OR "mass loss" OR "weight reduc*" OR "mass reduc*" OR weight near/1 reduc* OR "waist circumference" OR "waist-hip ratio" OR "waist to hip ratio" OR BMI OR "body mass index" OR "body fat" OR "adiposity" OR "fat reduc*" OR "fat loss")
NOT	Bariatric surgery	TS = ("bariatric surgery" OR "bariatric procedur*" OR "Roux-en-Y" OR "gastric band*" OR "sleeve gastrectomy" OR "gastric bypass" OR "gastroplasty" OR "jejunoileal bypass" OR "stomach stapl*")
Scopus	Dietary induced, intentional weight loss in people or animals	TITLE-ABS-KEY ("Weight Reduction Program*" OR {Reducing Diet} OR {Fat-Restricted Diet} OR {Carbohydrate-Restricted Diet} OR intentional OR {dietary intervention} OR {caloric restriction} OR {calorie restriction} OR {meal replacement} OR (diet w/1 restrict*))
AND	Chemical exposure	TITLE-ABS-KEY ("Chlorinated Hydrocarbon*" OR "Brominated Hydrocarbon*" OR "Fluorinated Hydrocarbon*" OR "Halogenated Hydrocarbon*" OR dioxin* OR {Dioxin-like} OR {Halogenated Diphenyl Ether} OR "Persistent Organic Pollutant*" OR Pesticide OR {Dibutyl Phthalate} OR {Diethylhexyl Phthalate} OR {Organotin Compound} OR Paraben OR "polychlorinated biphenyl*" OR "polyaromatic hydrocarbon*" OR Aroclor OR TCDD OR "polybrominated diphenyl ether*" OR "polybrominated diethyl ether*" OR PBDE* OR organochlorine* OR dichlorodiphenyltrichloroethane OR {dichlorodiphenyl trichloroethane} OR DDE OR dichlorodiphenyldichloroethylene OR {dichlorodiphenyl dichloroethylene} OR DDD OR heptachlor OR nonachlor OR HCB OR hexachlorobenzene OR pyrethroid OR "phenoxybenzoic acid" OR aldrin OR chlordan* OR dichlorvos OR mevinphos OR trichlorfon OR alachlor OR cyanazine OR dieldrin OR endrin OR hexachlorocyclohexane OR endosulfan OR PFAS OR PFOS OR {perfluorooctane sulfonic acid} OR PFOA OR {perfluorooctanoic acid} OR phthalate* OR MEHP OR DEHP OR bisphenol* OR BPA OR arsenic OR cadmium OR mercury OR tributyltin OR organotin OR triphenyltin OR triclocarban OR triclosan OR paraben* OR carbamate OR carbaryl OR furan* OR neonicotinoid* OR imidacloprid OR acetamiprid OR dinotefuran OR thiamethoxam OR clothianidin OR fipronil OR PM2.5 OR PM10 OR particulate OR ozone OR {nitrogen oxide} OR {nitrogen dioxide} OR {sulphur dioxide} OR {sulfur dioxide} OR {carbon monoxide} OR {black carbon} OR {polyaromatic hydrocarbon} OR PAH)
AND	Weight loss outcomes	TITLE-ABS-KEY ((weight loss) OR {mass loss} OR "weight reduc*" OR "mass reduc*" OR (weight w/1 reduc*) OR {waist circumference} OR {waist-hip ratio} OR {waist to hip ratio} OR BMI OR {body mass index} OR {body fat} OR adiposity OR "fat reduc*" OR {fat loss})
AND NOT	Bariatric surgery	TITLE-ABS-KEY (bariatric surgery OR bariatric procedur* OR "Roux-en-Y" OR "gastric band*" OR "sleeve gastrectomy" OR "gastric bypass" OR "gastroplasty" OR "jejunoileal bypass" OR "stomach stapl*")

(HbA1c), homeostatic model of assessment (HOMA) for insulin resistance (HOMA –IR), HOMA for β cell function (HOMA- β), glucose tolerance tests (GTTs), insulin tolerance tests (ITTs) and measures of liver fat content.

Controlled vocabulary and subject headings (e.g., MeSH) in PubMed were searched to identify additional keywords. The PubMed search strategy was exploded for use in Web of Knowledge and Scopus that do not use MeSH or other indexing terms or controlled vocabulary. No language or date limits were applied.

An initial, limited search to refine search terms was performed to ensure sensitivity and specificity and to identify any other index terms, common terms and synonyms for inclusion or exclusion [34]. New terms were only included if they expanded the number of relevant papers. Terms that only identified additional irrelevant papers were dropped from the search. The full search was then performed across all the databases on 17.4.2023 and again on 08.12.2023. Search results were downloaded and imported into Microsoft Excel (Version 2404) and Nested Knowledge (<https://nested-knowledge.com/>) for qualitative and quantitative synthesis. Duplicates were removed in Nested Knowledge.

2.2. Screening

Two evaluators independently screened the title and abstract of all retrieved citations against a set of minimum inclusion and exclusion criteria in Nested Knowledge. All articles identified as relevant by either evaluator were included in a full-text review. The two evaluators each independently assessed the articles to determine if they met the inclusion/exclusion criteria using dual screening in Nested Knowledge and Cohen's kappa was calculated [35]. Disagreements were resolved by discussion at adjudication. Studies were included if they 1. explored the effect of a known environmental contaminant, as listed in the search terms (Table 1); 2. if they examined intentional and diet-induced weight loss; 3. if they reported weight loss as an outcome. Any form of dietary induced intentional weight loss protocol was considered (e.g., fasting, calorie restriction; weight loss after high fat diet withdrawal). Studies in which animals were self-compared or in which they were compared to a control group were considered. We excluded any animal studies in which there was no unexposed weight loss group or condition to compare to exposed weight-loss individuals. We also excluded any study in which animals failed to lose weight on a food restriction regime, since such regimes were clearly still calorifically adequate.

References and citing publications of included papers were then searched. Connected Papers (<https://www.connectedpapers.com>) was used to identify other eligible papers from each included paper in the initial search and those identified from reference lists, which were then also subject to the same screening detailed above. After this initial screening phase, we subsequently excluded papers that examined contaminant redistribution or elimination during weight loss or assessed other toxicological markers since they did not set out to determine whether contaminants impacted either weight loss rate or glycemic control and thus reporting on the associations of interest was incidental or absent even when mass was measured.

2.3. Qualitative synthesis

A tagging hierarchy was developed, refined, and tested in Nested Knowledge and used to extract study characteristics in a standardised way. Study characteristics extracted included: bibliographic information (publication year, title, authors, publication type (e.g., original research) journal, digital object identifier (DOI)); study purpose; study design; animal characteristics: sex, age, strain and genetic background; chemical(s) examined; exposure route (e.g. gavage, dietary or intravenous or intraperitoneal injection); exposure dose, frequency and duration; diet intervention and duration; matrix used to assess exposure if performed (e.g. plasma, serum, whole blood, adipose; urine; faeces; hair); outcomes measured (e.g. body mass; adipose cell size; fasting

blood glucose; HOMA- β ; HOMA-IR; GTT; fasting insulin; HbA1c) and sample size. These data were abstracted by one evaluator and cross checked by the second evaluator, summarised and synthesised.

2.4. Risk of bias

Study quality, sensitivity, and risk of bias (RoB) was assessed by two evaluators using the SYStematic Review Centre for Laboratory animal Experimentation (SYRCL) tool for animal studies [36]. The signal questions were modified to ensure shared understanding of the question in this context for the evaluators. The updated signal questions were cross checked by all three authors before use and responses were collected in Office 365 forms. We summarised the data using RoBvis (<https://www.riskofbias.info/welcome/robvis-visualization-tool>) [37]. Five domains were considered: bias due to selection (e.g. rationale of strain/ species/ age class; randomisation of animals to groups and blinding process for allocation; comparability of animal characteristics between groups); bias due to study performance (e.g. housing; blinding of experimenters to groups; appropriate control group; comparability of animal handling between groups except for interventions; diet details; timing of exposure relative to caloric restriction); bias in outcome measurement (e.g. random selection of animals for measurement; blinding of assessors; timing of outcome measurements); bias due to missing data or attrition (e.g. completeness of reporting; comparability between groups in missing data; reasons for missing data; completion data reported; replacement of drop-outs); and bias in statistical handling or reporting (e.g. power analysis performed; appropriate techniques used; completeness of reporting of all outcomes; unit of analysis considerations). Domains in which any source of bias was limited or considered to have limited impact on the findings were rated as low and the results from the study were considered valid [38]. Domains at risk of some bias but not enough to invalidate the study results were rated moderate. Domains with significant risk of bias that may invalidate the study results were rated high. Disagreements on RoB and standardisation of rating between papers were resolved by discussion.

2.5. Quantitative analysis

2.5.1. A priori power estimation for meta-analysis

We performed a priori power analysis for the meta-analysis in R [39] version 4.1.1 (2021–08–10) “Kick Things”) using `dmetar` [40,41] assuming inclusion of 6 studies (K), which is typical in meta-analyses [42], and assuming a conservative sample size of 6 in each group (n1 and n2), since we expected groups to be balanced but likely of a small size typical of animal studies [43]. We assumed a random effects model would be implemented to allow for differences between study designs and calculated power for low, moderate and high heterogeneity and fixed p at 0.05. We calculated power for a range of effect sizes from 0.05 to 2 standardised mean difference between groups, since we had no prior knowledge of what typical effect sizes would be and a physiologically relevant effect size was difficult to estimate due to limited published research.

2.5.2. Data extraction

Raw data were not available for any of the studies that reported comparable study designs and outcomes and were suitable for meta-analysis. We therefore extracted data from graphs presented using Plotdigitiser freeware (<https://plotdigitizer.com/app>). We extracted body mass and glycemia control metrics (area under the curve (AUC) for both GTT and ITT), where these were reported. We extracted the available data for each subgroup per paper – for example where males and females or different knockouts or knockdowns were used in the same paper and exposed to the same treatment regimes. Both evaluators independently extracted the data [44]. The mean value and standard error for each comparison performed in each paper and the minimum sample size reported, where a single number was not reported, were

then used to calculate the standard deviation (sd) in each case. Where data were repeated across graphs, we extracted the data only once and using the graph that provided the clearest differentiation between groups.

2.5.3. Meta analysis

The mean and sd for each comparison were used to perform meta-analysis using `meta` [45] and produce a Forest plot in `metafor` [46] in R. In several instances one paper contributed more than one effect size to the meta-analysis because it reported on more than one experiment, an issue that would violate a key assumption and cause the ‘unit of analysis problem’ [42,47]. However, the animal models in each case were different, such that we can assume that there was no overlap between two experiments and no animal was used twice. Nevertheless, separate experiments within any one paper were not entirely independent but clustered because the authors and facilities for the two experiments were the same. We therefore assumed that the between-study heterogeneity was reduced, which can lead to false positive results. To deal with this clustering effect an aggregated effect size for each study was calculated by fitting a three-level meta-analysis using the `rma.mv` function in the `metafor` package. A random effects model was used to account for heterogeneity in sex and genotype between studies. The datasets and code are available in the Open Science Framework (OSF) [DOI <https://doi.org/10.17605/OSF.IO/N5R8S>].

3. Results

3.1. PRISMA

Identification, screening, and inclusion of records is outlined in Fig. 1. We retrieved 177 records after deduplication from databases, and a further 34 from searches of citing and cited papers and using Connected papers. The overlap between databases used and the source of included papers is shown in Fig. 2. 155 papers from databases were excluded after screening of the title and abstract. We were unable to obtain the full texts of four older papers identified through reference lists. Full text retrieval and screening of the remaining 22 papers from databases, resulted in exclusion of a further 19 papers (Fig. 1). Of the 34 full text papers that were identified through reference lists, citations and Connected Papers, all but 2 were excluded at full text screening stage because they were human studies, or ineligible animal studies. Agreement between reviewers after independent full text screening was 74 %. Cohen’s kappa was 0.43 [0.3, 0.57]. We were left with five eligible papers. Full screen and search details are provided in OSF (DOI <https://doi.org/10.17605/OSF.IO/N5R8S>).

3.2. Narrative review

A summary of the evidence is provided in Table 2 which shows the species, sample size, chemical groups assessed, the nature of the diet intervention and the key outcomes.

3.2.1. Study purpose

One paper that met our inclusion criteria intended to test the impact of chemical exposure on weight loss trajectory [48]. Four papers intended to examine the effect of chemical exposure on aspects of glycemic control [13;14;18; 48]. One paper stated the aim to be whether dichlorodiphenyltrichloroethane (DDT) and its metabolites attenuate improvements in lipid and energy homeostasis during calorie restriction after high fat diet, thus body mass was measured and reported as an outcome [49]. Three papers came from the same research group [13;14; 48] and used the same diet and exposure regime to examine different aspects of coplanar PCBs on metabolic control in a range of mouse models from the C57BL/6 strain. Details of the study design characteristics of the papers that tested the hypotheses of interest are provided in Table 3.

Each of the papers examining CB77 exposure in mice performed more than one experiment on different animal models. One [13] examined the effects of the coplanar PCBs (CB77 and CB126) on glucose and insulin homeostasis in lean and obese male mice. The second [14] examined whether the effect of CB77 on adipose inflammation and glucose homeostasis in lean male mice and obese male mice during weight loss is mediated by adipose aryl hydrocarbon receptor (AhR). The most recent [48] compared the effects of CB77 on weight loss and gain and glucose homeostasis between male and female mice that were either wild type or AhR knockout. Salter et al [18] examined whether PFOS prevents the beneficial effects of caloric restriction, including on liver fat and function, in male C57BL/6 mice.

3.2.2. Study design and sample size

In all studies, sample size was 5–10 animals per group in the final reported outcomes. In each case, animals were fed a high fat diet either with or without the chemical of interest and then placed on a weight loss diet. In four studies the initial diet was intended to induce obesity. It is unclear in [18] whether the initial weight gain was growth of young animals to full adult weight or intended to induce obesity prior to caloric restriction. All studies were longitudinal in design of the diet interventions (weight gain followed by restriction) and compared the chemical treatment groups with control unexposed groups subjected to the same diet interventions.

3.2.3. Animal characteristics

Four studies used young adult mice (2–4 months old) of the same genetic background (C57BL/6), but unknown substrains, and with a range of genetic modifications. Only one of the four mouse studies [48] included females. One study used young male adult (5 months) Sprague Dawley rats of the Charles River strain [49].

3.2.4. Chemical exposure

No studies examined emerging pseudopersistent chemicals such as phthalates and parabens with most focussed on chlorinated POPs. Three papers [13; 14; 48] examined the effects of coplanar PCBs, one examined DDT and its metabolite dichlorodiphenyldichloroethylene (DDE) [49] and one [18] examined the effect of the fluorinated compound PFOS. Four papers focussed on only one chemical, whereas Ishikawa et al used a mix of DDT and its metabolite DDE [49]. The chemical was a high purity analytical standard in each case and administered by gavage in all five papers rather than in the food or water or by injection.

Two coplanar PCBs (CB77 and CB126; Accustandard Inc, New Haven, CT, USA) were used in [13] at a range of concentrations in lean mice but this experiment did not include a diet-induced weight loss phase. We therefore focussed on the second experiment reported in this paper which used only CB77. Dioxin-like-PCBs (DL-PCB) are ligands for AhR, which is proposed to mediate their toxic effects, and CB77, a non-ortho-substituted tetrachlorobiphenyl (low chlorination state) that has dioxin-like properties, was used as a model AhR ligand and sourced from the same supplier in all three studies [13,14,48]. The dosing regimen used produced plasma levels after 48 h of the last dose comparable to those seen in human subjects exposed to high background levels and with elevated risk of T2DM [50]. The rationale for the discontinuous dosing in which an irregular dosage regime over 10 weeks in weeks 1 and 2, and 9 and 10 of a 12-week weight gain period, was not provided. All papers that explored the effect of CB77 did not continue the exposure during the weight loss phase. CB77 levels were measured after the full 16-week study in gonadal fat pads and liver of 3–4 animals per group and hydroxylated PCB metabolites were measured in plasma [48]. Measurements were performed against a CB77 or hydroxylated CB77 standard in acetonitrile extracted homogenates subject to solid phase extraction and analysed using gas chromatography coupled to tandem mass spectrometry (GC–MS/MS). The earlier studies [13,14] used the same approach but a different extraction process, and a different MS machine using only a CB209 standard.

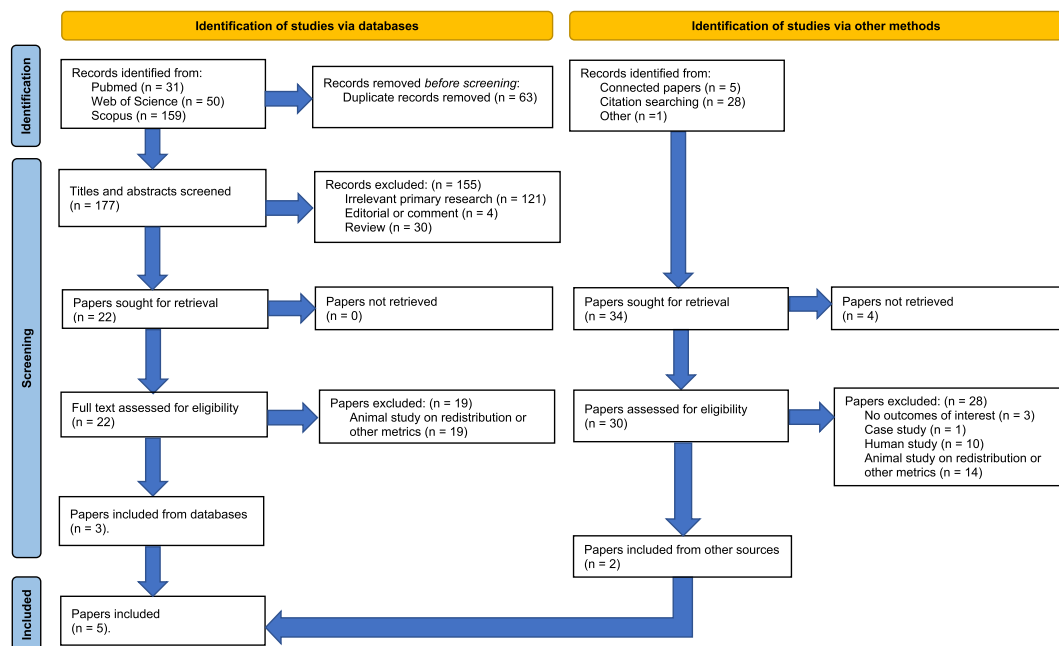


Fig. 1. PRISMA 2020 flow diagram [30] (Page et al 2021) showing outcome of searches of databases and other sources, screening and final inclusion of papers and studies.

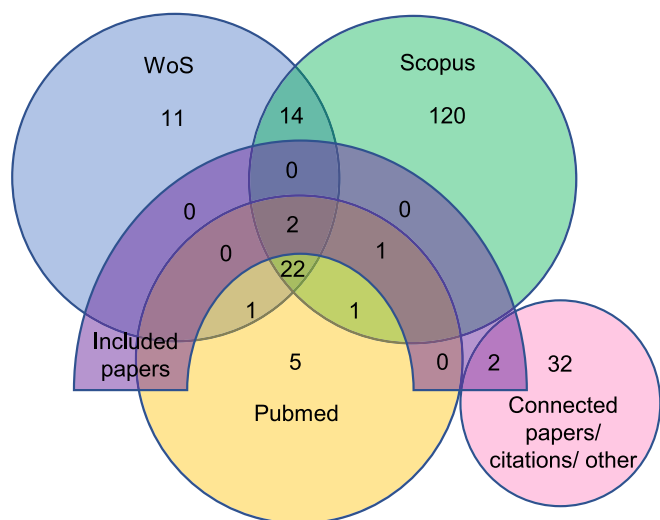


Fig. 2. Origin of the papers assessed in this study. Included papers are covered by the purple arc transecting the 3 overlapping ellipses and the independent circle that includes references list and Connected papers searches, which yielded papers that were not identified in the data base searches. WoS = web of science.

In the rat study [49] animals were dosed weekly by gavage during the high fat diet (HFD) phase of the study with a DDT (Accustandard Inc, New Haven, CT, USA) dose intended to mimic the cumulative exposure to DDT seen when rats were fed a high fat diet containing crude salmon oil rather than corn oil [51], which contained a mix of POPs. Tissue or blood levels of DDT were not measured. Dosing was not continued during the calorie restriction phase.

Male mice were exposed to PFOS (Sigma Aldrich, catalog no. 77282, Lot no. BCBH2834V, St. Louis, Missouri) daily during either *ad libitum* feeding or caloric restriction [18]. Exposure was thus simultaneous with the caloric restriction phase rather than allowing the chemical to accumulate prior to weight loss. The levels of PFOS were not measured to determine circulating or tissue specific concentrations. The dose rate was selected based on being lower than or similar to doses that produce no observable adverse effects (NOAEL) according to information from Agency for Toxic Substances and Disease Registry at the time of the study.

3.2.5. Diet interventions

In the three papers on CB77 the diet intervention was the same: 12 weeks of HFD to induce obesity followed by 4 weeks of a low-fat diet (LFD) to induce weight loss. The HFD phase produced body masses of ~ 45 g by week 14 compared to ~ 30 g in mice fed LFD over the same period [13], which is a biologically relevant 'excess' mass of ~ 50 %. Salter et al [18] fed the mice *ad libitum* on standard rodent chow for 5 weeks and then either a further 6 weeks *ad libitum* or 6 weeks of a 25 % calorie deficit compared to the *ad libitum* group. The body mass changes in the *ad libitum* fed mice was typical of mice of this strain and age as

Table 2

Summary characteristics of five papers included in a systematic review of evidence that contaminant exposure impairs weight loss and impedes resolution of glycaemic control during diet induced weight loss in animals. DDT = dichlorodiphenyltrichloroethane; PCBs = polychlorinated biphenyls; PFAS = per and poly fluoralkyl substances; GTT = glucose tolerance test; ITT = insulin tolerance test.

	Species		n	Diet intervention			Chemicals of interest			Outcomes			
	rat	mouse		High fat then food restriction	<i>Ad libitum</i> then food restriction	High fat then low fat	DDT	PCBs	PFAS	Mass	Other adiposity metrics	GTT	ITT
Number of studies	1	4	5	1	1	3	1	3	1	5	2	4	3

Table 3
Study characteristics for the five studies that intended to examine the effects of chemical exposure on mass loss and/ or glycaemic control.

Study	Species	Strain	Age	Sex	n	Chemical	Matrix	Dose regime	Dose rationale	Route	Diet	Diet duration
Jackson et al 2019 [48]	Mice	C57BL/6 background, from Jackson Laboratory (Stock # 002727). Includes wild type and AhR deficient (AhR $-/-$) mice	Young adult (2–4 mo)	M/ F	90 mice used; exp 1 AhR $+/+$ = 15F; 15 M controls; 15F; 16 M PCB77 exp 2 AhR $-/-$ = 9F 10 M PCB 77	CB77	Plasma; Liver; Epididymal or per-ovarian fat pad	50 mg kg^{-1} given 4 times: weeks 1, 2, 9 and 10 during HFD period.	As in [13]	Gavage	HFD (60 % calories as fat: D12492; Research Diets Inc.) <i>ad libitum</i> , followed by LFD (14.6 % calories as fat)	12 weeks of HFD (weight gain) to induce obesity followed by 4 weeks LFD (weight loss)
Baker et al 2013 [13]	Mice	C57BL/6 background	Young adult (2–4 mo)	M	N = 10/ group at start. N = 3 for tissue harvest at end of HFD. N = 7 in LFD intervention	CB77	Serum; Liver; Epididymal and retroperitoneal fat pad; Skeletal muscle	50 mg kg^{-1} given 4 times: weeks 1, 2, 9 and 10 during HFD.	Produces plasma levels of CB77 (48 h after the last dose) comparable with those seen in subjects from the Anniston Community Health Survey exhibiting a higher risk of T2DM [50].	Gavage	HFD (60 % calories as fat: D12492; Research Diets Inc.) <i>ad libitum</i> , followed by LFD (14.6 % calories as fat)	12 weeks of HFD (weight gain) to induce obesity followed by 4 weeks LFD (weight loss)
Baker et al 2015 [14]	Mice	C57BL/6 background. AhR deficiency induced in adipose using cre-lox compared to fl/ fl mice	Young adult (2–4 mo)	M	6–8 mice per group	CB77	Liver; epididymal fat pads;	50 mg kg^{-1} given 4 times: weeks 1, 2, 9 and 10 during HFD period.	As in [13]	Gavage	HFD (60 % calories as fat: D12492; Research Diets Inc.) <i>ad libitum</i> , followed by LFD (14.6 % calories as fat)	12 weeks of HFD (weight gain) to induce obesity followed by 4 weeks LFD (weight loss)
Ishikawa et al (2015) [49]	Rats	Sprague Dawley (obese Charles River)	Socially mature young adult (5 months) at start.	M	5–10 rats per group	DDT mix (DDT and DDE)	Not assessed	5.6 $\mu\text{g kg}^{-1}$ day $^{-1}$ given weekly	Produces a cumulative dose equivalent to either crude or refined salmon oil-supplemented chow	Gavage	HFD (45 % calories as fat/ moderate sugar: 20 % protein, 35 % carbohydrate (17 % sucrose): D12451, Research Diets, New Brunswick, NJ) <i>ad libitum</i> , followed by 60 % calorie reduction on standard chow	4 weeks on HFD and 2 weeks on calorie restriction
Salter et al 2021 [18]	Mice	C57BL/6 background	Young adult. 10 week old at purchase. 15 weeks when mass stable; 21 weeks at start of caloric restriction	M	8 mice per group	Heptadeca-PFOS	Not assessed	Daily 100 mg kg^{-1} , 5 ml kg^{-1}	Lower or similar to doses that produce no observable adverse effects according to most recent information from Agency for Toxic Substances and Disease Registry	Gavage	<i>Ad libitum</i> purified rodent chow (AIN-93G Growth Purified Diet) then <i>ad libitum</i> or 25 % calorie restricted on same food.	5 weeks <i>ad libitum</i> then 6 weeks <i>ad libitum</i> or 25 % calorie restricted

they gain weight on standard chow, and body mass remained around 30 g, such that the diet did not cause excess mass accumulation prior to food restriction. Rats in [49] were fed for 4 weeks on a high fat, moderate carbohydrate diet, but the fat content was 45 % compared to the 60 % fat used in the CB77 mouse studies. Charles River Sprague Dawley rats are heavier and fatter than other strains. Nevertheless, these animals gained further weight of around 6–10 %, from ~ 680–690 g after a standard rat chow diet for 3 months, to 725–740 g during the HFD period. The animals were then placed on a standard chow diet that provided 60 % of their previous *ad libitum* HFD intake, which was intended to model the rapid 20–25 % weight loss seen in people after bariatric surgery, but returned their weight to a level similar to that at the start of the study.

3.2.6. Outcomes measured

Glucose control was tested using two approaches. The ability of the animals to respond appropriately to a bolus injection of glucose after an overnight fast by reducing glucose back to baseline tests the capacity to secrete insulin from pancreas and is termed a GTT. ITTs explore the ability of the animal to reduce glucose levels in response to externally administered insulin, an indicator of insulin sensitivity of the tissues. Body mass or mass change and a GTT after a 6 or 12 h fast was measured in all the four mouse studies. Additional adiposity measures or fasting insulin/ ITT (after 4 h fasting) were performed in two of the mouse studies. In the studies on CB77, body weight of each mouse was measured weekly [13; 14; 48]. Body composition was measured by NMR in two of these [14; 48] and was performed at baseline and study endpoint in both, but additionally after HFD weight gain on each mouse in [48]. Timing of the glycemia control measurements differed between studies. GTT and ITT were performed in weeks 4 and 12 of HFD phase and the final week of the LFD phase (week 16) in [13], whereas these tests were performed only after the LFD phase in [14]. GTT was performed in week 11 and week 13 during the HFD and LFD periods, respectively in [48], but ITT was not undertaken. Adipocyte size was quantified at the study endpoint in [14], but not in the other CB77 studies.

Salter et al measured body weight and food intake daily, GTT after 3 weeks of calorie restriction and ITT after 4 weeks [18]. Ishikawa et al [49] measured mass of the rats three times weekly.

3.2.7. Reported findings

CB77 treated mice did not gain weight faster during HFD than vehicle-treated control [13]. CB77 dose-dependently reduced the ability of lean mice and low-fat fed mice to lower their glucose levels when presented with a glucose challenge (GTT) and reduced their sensitivity to insulin (ITT). When animals were given HFD, this glucose regulation disruptive effect of CB77 was no longer apparent, perhaps because the control animals also had impaired glucose tolerance and insulin sensitivity [13]. Although all calorie restricted animals in this paper showed improved glucose and insulin tolerance compared to the HFD phase, the CB77 treated animals showed less improvement in these measures compared to vehicle treated individuals [13]. To explore this further, an adipose specific AhR knock out mouse was produced using Cre-lox technology [14]. Adipocyte-specific AhR deficient mice (AhR^{ADQ}) gained more fat mass and less lean mass than mice without the cre-lox induced deficiency (AhR^{fl/fl}) when fed a standard diet, but this did not lead to overall differences in body mass, whereas the difference in body mass and composition was marked after high fat diet, with greater subcutaneous fat in AhR^{ADQ} mice [14]. CB77 administration prevented the increased fat deposition during the HFD phase in the AhR^{ADQ}. Consistent with [13], CB77 did not cause a difference in glucose tolerance or insulin sensitivity during HFD in either AhR^{fl/fl} or AhR^{ADQ} [14]. When CB77 treated AhR^{fl/fl} mice lost mass during the LFD phase, their ability to cope with a glucose load or respond to insulin administration was diminished compared to the vehicle treated controls. In contrast, there was no difference in the glucose tolerance or insulin sensitivity of

vehicle or CB77 treated AhR^{ADQ} mice, suggesting AhR is needed for the metabolic/ endocrine effect of CB77. Adipose CB77 levels were higher in the AhR^{ADQ} mice than in the AhR^{fl/fl} mice after HFD but hydroxylated CB77 was not different between genotypes. Adipose levels of CB77 dropped in both genotypes and hydroxylated CB77 levels increased but were lower in the AhR^{ADQ} mice than in the AhR^{fl/fl} mice after weight loss, suggesting greater elimination of CB77 in adipose-specific AhR knockdown animals.

Male mice fed HFD had higher fat mass and lower lean mass than females [48], irrespective of CB77 or vehicle treatment. CB77 treatment did not alter mass gain trajectory or final mass, body composition or glucose tolerance in male mice, whereas female mice treated with CB77 gained less mass and less fat than vehicle treated controls, but showed no difference in glucose tolerance during HFD. In wild type animals body weight, fat mass and lean mass were not different in either sex after the LFD irrespective of treatment. Consistent with previous studies [13,14], the wild type male mice treated with CB77 showed impaired glucose tolerance during weight loss compared to the vehicle controls, but female wild type mice showed no effect of CB77. During weight loss, AhR^{-/-} females treated with CB77 had a reduced ability to deal with a glucose load than AhR^{-/-} controls, and compared to AhR^{+/+} females given CB77. Males showed the opposite effect: AhR^{-/-} male mice administered CB77 coped better with a glucose load than AhR^{+/+} males administered CB77. Males and females did not differ in liver or adipose levels of CB77. All of these data suggest there is a sex difference in sensitivity of glucose homeostasis to CB77 that depends on the presence of AhR. CB77 levels were higher in AhR^{-/-} mice than wild type mice of both sexes. There were a range of sex differences in tissue specific gene expression of targets involved in glucose homeostasis that may have contributed to the sex and genotype differences observed. These three studies provide consistent evidence for a sex specific effect of coplanar PCBs on glucose homeostasis, but not weight loss, that manifests during calorie restriction, suggesting males may experience a greater impairment than females, dependent on AhR.

Body mass was used to calculate food conversion efficiency (weight gained per energy consumed per week) in study of DDT effects in rats [49]. Of particular note, the rate of weight gain was lower during HFD, and rate of weight loss was greater during the calorie restriction phase in the DDT treated animals compared to unexposed controls. Lack of other studies on DDT preclude a meta-analysis.

Vehicle and PFOS treated mice showed similar changes in body and tissue mass during *ad libitum* feeding and caloric restriction [18]. The calorie restricted mice reduced body mass from 30–32 g to ~ 25–28 g, such that absolute changes in body mass, and differences relative to the *ad libitum* group were ~ 12–25 %. PFOS did not alter the response to GTT in *ad libitum* fed mice. However, PFOS treated calorie restricted-mice experienced higher glucose levels than vehicle treated controls 1 and 2 h after a glucose challenge, suggesting development of glucose intolerance. In addition, PFOS treated mice had higher glucose levels after insulin challenge than vehicle treated animals in both *ad libitum* and calorie restricted groups. These data suggest PFOS induced insulin resistance irrespective of feeding state and even in mice without overt obesity. Lack of any other studies on PFOS in this context prevents a meta-analysis.

3.3. Risk of bias

The risk of bias for each of five domains and overall study risk of bias in the five studies that directly answered our question of interest is presented in Fig. 3 and the rationale for each rating is given in Table 4. Assessment details from each reviewer and consensus are available in OSF (DOI <https://doi.org/10.17605/OSF.IO/N5R8S>). All five studies were at moderate risk of bias from selection, study performance, outcome measurement, and low to moderate risk in statistical analysis, largely because of lack of reported detail. Two studies had a serious risk of bias due to missing data for which insufficient information was

provided, one had moderate risk of bias because animal deaths in the control group were addressed by adding more animals to each group, but the reasons for the deaths were not adequately explained and could have related to unreported differences in handling between groups. Two papers were at low risk of bias because all animals were followed and reported on throughout.

3.4. Meta analysis

3.4.1. A priori- power calculation

A priori power estimation for six independent studies each with a sample size of 6 in each group and $p = 0.05$ (Table 5) indicate that a power of 0.8 or greater is achievable for meta-analysis with a pooled effect size of $d = 0.8$, $d = 0.9$ and $d = 1.0$ and above for meta-analysis with low, medium and high heterogeneity, respectively.

3.4.2. Meta analysis

All the animals in the studies on CB77 [13,14,48] were mice with the same genetic background and received the same chemical and diet treatment, irrespective of sex and AhR status, and the papers each included more than one study group. It was therefore possible to undertake a meta-analysis on several outcomes from the different experimental groups within the papers, even though the number of papers was lower than our expected $K = 6$. Important caveats to the interpretation of this meta-analysis are that all the data were derived from the same research group and the sample size in each case was small and not always clearly reported. In addition, there are likely to be some inaccuracies in the numbers we report compared to the original studies because the data were extracted from graphs and lack of specificity in reporting of sample size meant we had to use the lowest sample size reported across groups, to ensure a conservative estimate, to calculate standard deviation for estimation of pooled confidence intervals.

3.4.2.1. Mass. We extracted final mass from five different animal models tested across the three papers. The pooled mean differences between vehicle and PCB treatment are shown in Fig. 4. There was no significant effect of CB77 treatment on final mass across wild type males and females and in both normal floxed males and those that exhibited AhR deficiency in adipose (standardised mean difference = -0.35 [$-1.09, 0.39$]). Heterogeneity was low and did not differ between animal models ($I^2 = 0$; $\tau^2 = 0$; $Q = 1.58$; $p = 0.813$). We were unable to extract the data for AhR $-/-$ females from [48] because the presentation in the graphs did not allow us to differentiate between groups. Mass loss rate data were not presented in [14] and the data presented in the graphs in [48] did not allow the different groups to be easily disentangled visually to facilitate data extraction and this prevented meta-analysis of mass loss rates or total mass change, which may be more sensitive measures than final mass. Effect sizes for final mass ranged from 0 to 0.71. To detect a real effect of these magnitudes with 80 % power would require very large sample sizes.

3.4.2.2. GTTs. GTTs a way to measure the ability to clear a glucose load through appropriate secretion of insulin, were performed in the animals in all three papers, and this allowed us to extract AUC data for 6 different animal models. No data were presented in [48] for male vehicle treated AhR $-/-$ mice. The pooled mean differences between vehicle and PCB treatment in the remaining six animal models are shown in Fig. 5. Vehicle treated animals had lower mean AUC in GTTs compared with CB77 treated animals across animal models (standardised mean difference = -1.30 [$-1.896, -0.63$]), such that CB77 treated mice had glucose intolerant compared to controls. Inspection of the Forest plot shows that the difference was largely driven by the male mice with intact AhR. However, the direction of effect was consistent across all animal models. Effect sizes for the GTT tests ranged from 0.87 to 2.16. Heterogeneity was low and did not differ between animal models ($I^2 = 0$; $\tau^2 = 0$; $Q = 2.91$; $p = 0.714$).

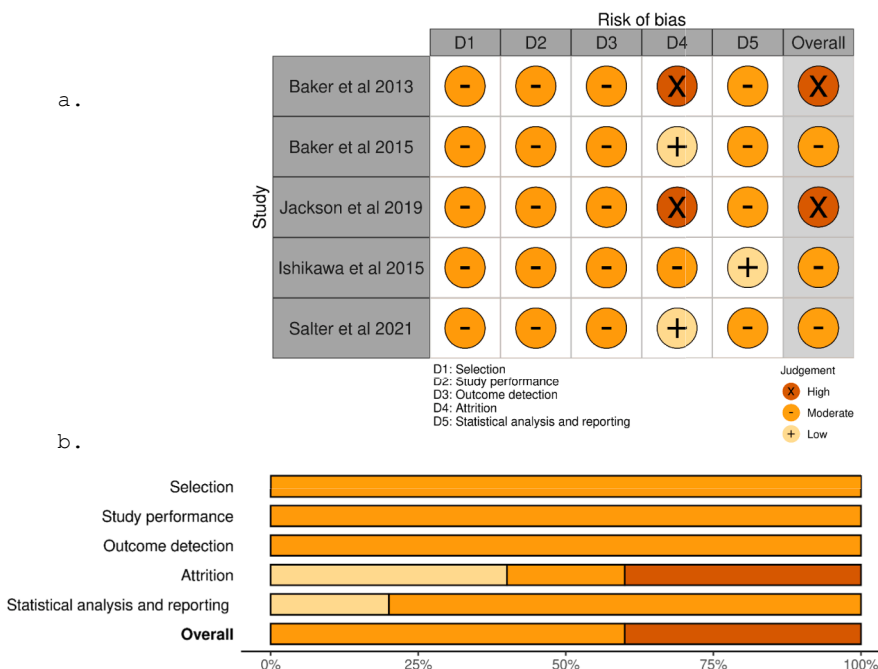


Fig. 3. Traffic light (a) and unweighted summary (b) plots for Risk of Bias assessed using the SYRCLE tool [36] (Hoojijmans et al 2014) in five domains for the five studies that addressed the hypothesis that contaminant exposure may affect success of weight loss or glycemic control resulting from dietary calorie restriction intervention. Overall risk is taken as the highest rating from any domain: D1 = bias due to selection; D2 = bias due to study performance; D3 = bias due to detection of outcome; D 4 = bias due to attrition; D5 = bias due to reporting and statistical analysis. Dark shade with x indicates high risk of bias; mid shade with – indicates moderate risk of bias; pale shade with + indicates low level of risk. Summary plot indicates what proportion of studies fall into each risk category for each domain. Produced using RobVis [37] (McGuinness et al 2020).

Table 4

Risk of bias assessment using the SYRCL tool [36] for the five studies that addressed the potential association between contaminant exposure and weight loss or glycaemic control for each of five domains indicated in the lefthand column. Each cell provides a synopsis of consensus responses to bespoke signal questions within each domain (see OSF: DOI 10.17605/OSF.IO/N5R8S) that were modified from the SYRCL tool for the specific review question addressed in this study to ensure shared understanding of each question in this context. They are arranged to allow comparison between studies for each aspect considered.

	Baker et al 2013 [13]	Baker et al 2015 [14]	Jackson et al 2019 [48]	Ishikawa et al 2015 [49]	Salter et al 2021 [18]
Selection	Moderate concern: Allocation method of animals to specific groups is not reported so it is not possible to assess whether it was randomly generated or concealed from those performing the experiments	Moderate concern: Allocation method of animals to specific groups is not reported. The paper states that animals were randomly assigned but the mechanism is not provided. It is not clear whether allocation was concealed from those performing the experiments	Moderate concern: Allocation method of animals to specific groups is not reported. The paper states that animals were randomly assigned but the mechanism is not provided. It is not clear whether allocation was concealed from those performing the experiments	Moderate concern: Allocation method of animals to specific groups is not reported. The paper states that animals were randomly assigned but the mechanism is not provided, and animals seem to have been allocated to provide a comparable starting mass and lipid profile. It is not clear whether allocation was concealed from those performing the experiments	Moderate concern: Allocation method of animals to specific groups is not reported. The paper states that animals were randomly assigned but the mechanism is not provided, and animals seem to have been allocated to provide a comparable starting mass. It is not clear whether allocation was concealed from those performing the experiments
	Moderate concern: Characteristics of the animals in each group at the start were partly reported, including age and sex, which was constant. However, mass of animals and glycaemia control indices in each group at the start of the trial or at start of the low-fat diet were not reported. It is thus unclear if animals in each group were similar for all important outcomes at the start of the experiment or whether confounds needed to be accounted for in analysis.	Moderate concern: Characteristics of the animals in each group at the start were partly reported, including age and sex, which was constant. The paper states that animals were the same based on external appearance at the start and data presented show no difference in mass but a difference in fat accumulation between groups. GTT and ITT show no difference, but some morphometrics not the same.	Moderate concern: Characteristics of the animals in each group at the start were partly reported, including age and sex, which was constant. AhR ^{-/-} females were lighter than AhR ^{+/+} females at start. Statistical differences at the start of high-fat or low-fat diets were described but not controlled for.	Moderate concern: Characteristics of the animals in each group at the start were partly reported, including age and sex, which was constant. No information is provided on glycaemia control indices but this was not an outcome measured in the study	Moderate concern: Characteristics of the animals in each group at the start were partly reported, including age and sex, which was constant. Mass was the same across groups at the start, but equivalent glycaemia status is not reported
	Moderate concern: It is unclear how subsets of animals for sacrifice or for insulin treatments were selected	Moderate concern: It is unclear how subsets of animals for different outcome measures were selected	Moderate concern: It is unclear how subsets of animals for different outcome measures were selected	Low concern: all animals were assessed for all outcomes	Low concern: all animals were assessed for all outcomes
	Low concern: Reasons for the species and strain used were not provided	Low concern: Reason for the adipose specific AhR knockdown and its control are given but not the genetic background of the mouse strain	Low concern: Reason for the AhR ^{-/-} and ^{+/+} are given but not the genetic background of the mouse strain	Low concern: reason for the strain were provided	Low concern: Reasons for the species and strain used were not provided
Study performance	Moderate concern: Housing of animals is unclear in terms of random allocation to cages or positioning and cycling of cages. It is also unclear if animals were housed together or individually.	Moderate concern: Housing of animals is unclear in terms of random allocation to cages or positioning and cycling of cages. It is also unclear if animals were housed together or individually.	Moderate concern: Housing of animals is unclear in terms of random allocation to cages or positioning and cycling of cages. It is also unclear if animals were housed together or individually.	Moderate concern: Housing of animals is unclear in terms of random allocation to cages or positioning and cycling of cages. Animals were housed individually and this could add social stress for a gregarious species	Moderate concern: Housing of animals is unclear in terms of random allocation to cages or positioning and cycling of cages. It is also unclear if animals were housed together or individually.
	Moderate concern: It is unclear whether caregivers and experimenters were blind to the treatment the animals received	Moderate concern: It is unclear whether caregivers and experimenters were blind to the treatment the animals received	Moderate concern: It is unclear whether caregivers and experimenters were blind to the treatment the animals received	Moderate concern: It is unclear whether caregivers and experimenters were blind to the treatment the animals received	Moderate concern: It is unclear whether caregivers and experimenters were blind to the treatment the animals received
	No concern: An appropriate control group was used in the tests relevant to this review and the control group were treated in the same way as the exposed groups	No concern: An appropriate control group was used in the tests relevant to this review and the control group were treated in the same way as the exposed groups	Moderate concern: One of experiments has no male vehicle group to compare the PCB treatment to.	No concern: An appropriate control group was used in the tests relevant to this review and the control group were treated in the same way as the exposed groups	No concern: An appropriate control group was used in the tests relevant to this review and the control group were treated in the same way as the exposed groups
	Low concern: Since animals were fed by gavage it seems unlikely animals did not receive the vehicle or exposure treatment	Low concern: Since animals were fed by gavage it seems unlikely animals did not receive the vehicle or exposure treatment	Low concern: Since animals were fed by gavage it seems unlikely animals did not receive the vehicle or exposure treatment	Low concern: Since animals were fed by gavage it seems unlikely animals did not receive the vehicle or exposure treatment	Low concern: Since animals were fed by gavage it seems unlikely animals did not receive the vehicle or exposure treatment

(continued on next page)

Table 4 (continued)

	Baker et al 2013 [13]	Baker et al 2015 [14]	Jackson et al 2019 [48]	Ishikawa et al 2015 [49]	Salter et al 2021 [18]
	<p>Moderate concern: The dietary information has little detail. While the product number is given and the percentage fat for both low and high fat diets is reported, the timing of the meals is not provided. Given mice may have been housed in groups and food intake was not recorded individually it is not clear how the amount of food eaten by each animal was controlled or recorded. If the PCB treated animals ate more to achieve the same weight, this would not be apparent</p> <p>No concern: In all cases exposure to the chemical occurred prior to the onset of the weight loss period.</p>	<p>Moderate concern: The dietary information has little detail. While the product number is given and the percentage fat for both low and high fat diets is reported, the timing of the meals is not provided. Given mice may have been housed in groups and food intake was not recorded individually it is not clear how the amount of food eaten by each animal was controlled or recorded. If the PCB treated animals ate more to achieve the same weight, this would not be apparent</p> <p>No concern: In all cases exposure to the chemical occurred prior to the onset of the weight loss period.</p>	<p>Moderate concern: The dietary information has little detail. While the product number is given and the percentage fat for both low and high fat diets is reported, the timing of the meals is not provided. Given mice may have been housed in groups and food intake was not recorded individually it is not clear how the amount of food eaten by each animal was controlled or recorded. If the PCB treated animals ate more to achieve the same weight, this would not be apparent</p> <p>No concern: In all cases exposure to the chemical occurred prior to the onset of the weight loss period.</p>	<p>Low concern: Moderate concern: The dietary information has little detail. While the product number is given and the percentage fat is reported, the timing of the meals is not provided. Nevertheless, animals were housed individually and food intake recorded to allow calculation of food efficiency.</p> <p>No concern: In all cases exposure to the chemical occurred prior to the onset of the weight loss period.</p>	<p>Moderate concern: The dietary information has little detail. While the product number is given and the percentage fat for both low and high fat diets is reported, the timing of the meals is not provided. Given mice may have been housed in groups and food intake was not recorded individually it is not clear how the amount of food eaten by each animal was controlled or recorded. If the PFOS treated animals ate more to achieve the same weight, this would not be apparent</p> <p>Low concern: it is unclear whether the weight loss diet commenced prior to or concomitant with the exposure to PFOS. PFOS exposure was maintained throughout weight loss</p>
Detection	<p>Moderate concern: It is unclear how animals were selected for outcome measurement since only a subset of the total sample size were used in some of the outcome measurements. For example, how 3 animals were selected for sacrifice prior to onset of the weight loss diet and how animals were selected for the tolerance tests is unclear</p> <p>Moderate concern: Efforts to blind the assessors to animal treatment group are not reported and neither are efforts to randomise order of sampling.</p> <p>Moderate concern: time of day and timing relative to meals of mass and other measurements is not reported. Timing of glucose tolerance tests and insulin tolerance tests were after a fixed fast duration and was consistent.</p> <p>Moderate concern: a glucometer was used for measurement of plasma glucose. Settling rate of red blood cells can differ between species and thus human glucometers can provide false results when used in other species without validation. The Freestyle freedom lite complies with ISO standards for accuracy and gives reading within 20% of the true value at 15mg/dl [96]. Its performance in mice is unknown</p>	<p>Moderate concern: It is unclear how animals were selected for outcome measurement since only a subset of the total sample size were used in some of the outcome measurements. For example, it is unclear how the mice for adipocyte measurements were chosen and how the slides were chosen from the number available.</p> <p>Moderate concern: Efforts to blind the assessors to animal treatment group are not reported and neither are efforts to randomise order of sampling.</p> <p>Low concern: Timing of measurements given and consistent including time after fasting for mass and GTT/ ITT.</p> <p>Moderate concern: method for glucose measurement is not reported</p>	<p>Moderate concern: It is unclear how animals were selected for outcome measurement since sample size is not always clearly reported</p> <p>Moderate concern: Efforts to blind the assessors to animal treatment group are not reported and neither are efforts to randomise order of sampling.</p> <p>Moderate concern: time of day and timing relative to meals of mass and other measurements is not reported. Timing of glucose tolerance tests and insulin tolerance tests were after a fixed fast duration and was consistent.</p> <p>Low concern: a glucometer (AccuChek) was used for measurement of plasma glucose which was different from that used previously by the same research group [13], but also complies with ISO standards for accuracy [96] and has been tested for accuracy when used with plasma or serum in this strain of mice [97].</p>	<p>Low concern: all animals underwent all measurements</p> <p>Moderate concern: Efforts to blind the assessors to animal treatment group are not reported and neither are efforts to randomise order of sampling.</p> <p>Moderate concern: time of day and timing relative to meals of mass and other measurements is not reported. Other measurements are not outcomes of interest here but their timings were standardised</p>	<p>Low concern: all animals underwent all measurements</p> <p>Moderate concern: Efforts to blind the assessors to animal treatment group are not reported and neither are efforts to randomise order of sampling.</p> <p>Moderate concern: time of day and timing relative to meals of mass and other measurements is not reported. Timing of glucose tolerance tests and insulin tolerance tests were after a fixed fast duration and was consistent.</p> <p>Low concern: a glucometer (Bayer Contour) was used for measurement of plasma glucose which was different from that used by other research groups and does not comply with ISO standards [96] but has been tested for accuracy when used with plasma or serum in this strain of mice [97].</p>
Attrition	<p>Serious concern: There is evidence for some missing data and the reasons are not explained. There were 10 animals per</p>	<p>Low concern: sample size is reported at 6-8 and this remains constant throughout the paper such that it is unlikely that</p>	<p>Serious concern: There is evidence for some missing data and the reasons are not explained. The original study uses</p>	<p>Moderate concern: Missing data is acknowledged. Reasons for animal death is not provided but is all in control group</p>	<p>No concern: no missing data and sample sizes are consistent</p>

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Table 4 (continued)

	Baker et al 2013 [13]	Baker et al 2015 [14]	Jackson et al 2019 [48]	Ishikawa et al 2015 [49]	Salter et al 2021 [18]
	group at the start. Three were killed at the end of the high fat diet. The remainder should appear in the data but only n = 5 appear in the glucose and insulin tolerance tests with no explanation for drop out. Sample size in figure S7 is vague so it is unclear if all 7 animals are present at each time point in each group because n is greater than or equal to 5.	there are missing data but uncertainty over sample size per group is a potential concern.	15/ 16 animals at start in Ahr +/-mice for vehicle and control and then 9/10 for the Ahr deficient animals. No information is given on drop out but the final sample sizes are 6-10 animals and we don't know how many in each group. The best case scenario is 6 of 9 and 10 of 15 and the worst is 6/16 and none of these is 80% or higher	in an initial cohort and is unlikely due to the experiment. However, if it is due to husbandry it could drive differences between groups. Masses of the animals that died are not included in analysis.	
	Serious concern: Less than 80% of the initial animals (either 10 or 7) were followed up in each group	Low concern: it appears that more than 80% of animals (in fact 100% of animals) were followed up	Serious concern: Less than 80% of the initial animals were followed up in each group	Moderate concern: 100% of the DDT but only 70% of the control group were followed up.	No concern: 100% follow up
	Low concern: Missing data appear similar across groups because the same number from each group are used in subsets.	Low concern: sample size does not vary but there is lack of clarity over how many per group and reason for difference.	Low concern: Missing data appear similar across groups because the same number from each group are used in subsets.	Moderate concern: sample size is consistent throughout but impact of lower number in controls is unclear	No concern: sample size is the same between groups and no dropouts
	Moderate concern: It is unclear whether missing data are related to the diet or exposure because details are not provided	Low concern: since there is no missing data, exposure or diet cannot be a reason for drop out here	Moderate concern: It is unclear whether missing data are related to the diet or exposure because details are not provided	Moderate concern: lack of 3 animals in controls is unlikely due to treatment effects but bias in husbandry effects leading to death could mask true effects of DDT.	Low concern: since there is no missing data, exposure or diet cannot be a reason for drop out here
	No concern: no new animals were added to the study	No concern: no new animals were added to the study	No concern: no new animals were added to the study	Low concern: an additional cohort was added but this is because controls would have only 2 animals after deaths, so this increased overall sample size. An equal number of animals were added to each group.	No concern: no new animals were added to the study
Statistics and reporting	Moderate concern: No power analysis was reported. For example, at 12 weeks of high fat diet the ability to see a difference in glucose tolerance test response may be limited because of high degree of variance in the PCB treated animals. This large variance means the difference would have to be very large to detect it. The absolute difference in AUC for glucose in the 12-week high fat fed animals is of greater magnitude than the significant difference later at 16 weeks such that the PCB treated animals may have had differences in their glycaemic control at the start of the high fat diet compared to vehicle as well as at the end.	Moderate concern: No power analysis was reported.	Moderate concern: No power analysis was reported.	Low concern: No power analysis was reported. Differences were observed between groups at this sample size showing effects could be detected at this sample size.	Low concern: power analysis was performed
	Low concern; the statistical section in the methods is clear and statistics are appropriate, but it is unclear whether a random effect for slope as well as intercept was used	Low concern; the statistical section in the methods is clear and statistics are appropriate, but it is unclear whether a random effect for slope as well as intercept was used	Low concern; the statistical section in the methods is clear and statistics are appropriate but it is unclear whether a random effect for slope as well as intercept was used	Low concern; the statistical section in the methods is clear and statistics are appropriate. A random effect was included per individual to account for longitudinal measures. It is unclear whether a random effect for slope as well as intercept was used	Moderate concern; the statistical section in the methods is clear and statistics are appropriate but it is unclear whether a random effect for slope as well as intercept was used. Repeated measures analysis should have been performed on GTT and ITT data

(continued on next page)

Table 4 (continued)

Baker et al 2013 [13]	Baker et al 2015 [14]	Jackson et al 2019 [48]	Ishikawa et al 2015 [49]	Salter et al 2021 [18]
Low concern: no protocol was available but methods and results match in terms of outcomes reported.	Low concern: no protocol was available but most of the methods and results match. No information on adipocyte size after weight loss in the groups is reported. Figure S4 only reports final mass not mass change trajectory.	Low concern: no protocol was available but methods and results match in terms of outcomes reported.	Low concern: no protocol was available but methods and results match in terms of outcomes reported.	Low concern: no protocol was available but methods and results match in terms of outcomes reported.
Moderate concern: Since it is unclear how animals were housed (together or in separate cages) it is possible that the study has over estimated n by using individuals and not cages as the unit of analysis	Moderate concern: Since it is unclear how animals were housed (together or in separate cages) it is possible that the study has over estimated n by using individuals and not cages as the unit of analysis	Moderate concern: Since animals were housed 3-5 to a cage, it is possible that the study has over estimated n by using individuals and not cages as the unit of analysis	Low concern: there are no unit of analysis issues because animals were individually housed	Moderate concern: Since it is unclear how animals were housed (together or in separate cages) it is possible that the study has over estimated n by using individuals and not cages as the unit of analysis
Low concern: the reported effect is unlikely to be a result of selection of reporting of multiple outcomes or multiple analyses.	Low concern: the reported effect is unlikely to be a result of selection of reporting of multiple outcomes or multiple analyses. Absence of reported adipose dimensions after weight loss may be from too few animals at the end of the study to subset further.	Low concern: the reported effect is unlikely to be a result of selection of reporting of multiple outcomes or multiple analyses.	Low concern: the reported effect is unlikely to be a result of selection of reporting of multiple outcomes or multiple analyses.	Low concern: the reported effect is unlikely to be a result of selection of reporting of multiple outcomes or multiple analyses.
Moderate concern: it is possible that the effect reported is due to selection of individuals in a subgroup that showed the most dramatic difference in results between groups because the reason for the subgroup reporting is not provided.	Low concern: the effect reported is unlikely to be due to selection of individuals in a subgroup that showed the most dramatic difference in results because all animals appear to be included.	Moderate concern: it is possible that the effect reported is due to selection of individuals in a subgroup that showed the most dramatic difference in results between groups because the reason for the subgroup reporting is not provided.	Low concern: all animals were included so subgroup analysis was not performed	Low concern: all animals were included so subgroup analysis was not performed
Low concern: the study was free of inappropriate influence from funders because authors state they have no conflict of interest and funding is a government grant.	Low concern: the study was free of inappropriate influence from funders because authors state they have no conflict of interest and funding is a government grant.	Low concern: the study was free of inappropriate influence from funders because authors state they have no conflict of interest and funding is a government grant.	Low concern: the study was free of inappropriate influence from funders because authors state they have no conflict of interest and funding is a government grant.	Low concern: the study was free of inappropriate influence from funders because authors state they have no conflict of interest and funding is a government grant.
Low concern: The study was published after the original ARRIVE guidelines [87] but likely prior to widespread uptake and expectations for publication	Low concern: The study was published after the original ARRIVE guidelines [87] but perhaps prior to widespread uptake and expectations for publication	Moderate concern: The study was published after the original ARRIVE guidelines [87] and during a period of wider uptake and expectations for publication. The journal appears to have encouraged use of the ARRIVE checklist in at least 2013 [98] well before the publication date for this paper	Low concern: The study was published after the original ARRIVE guidelines [87] and during a period of wider uptake and expectations for publication. The current guidelines from the journal require this to be stated but it is unclear what was required at the time.	Low concern: The study was published after the original and more recent ARRIVE guidelines [87] and during a period of wide uptake and expectations for publication, but these do not appear to be required for the journal here.

Table 5

Power analysis for meta-analysis assuming a random effects model at low, moderate and high heterogeneity, number of studies (K) = 6, number of animals per group = 6 and $p = 0.05$. Shading represents where the power to detect an effect of the given size is greater than 0.8.

Effect size	Power		
	Low	Moderate	High
0.1	0.07	0.06	0.06
0.2	0.11	0.10	0.09
0.3	0.20	0.17	0.15
0.4	0.31	0.26	0.22
0.5	0.44	0.37	0.31
0.6	0.58	0.49	0.42
0.7	0.71	0.61	0.53
0.8	0.81	0.71	0.64
0.9	0.88	0.80	0.73
1	0.93	0.87	0.81
1.1	0.96	0.92	0.87
1.2	0.98	0.85	0.91
1.3	0.99	0.97	0.94
1.4	1	0.98	0.96
1.5	1	0.99	0.98
2	1	1	1

3.4.2.3. ITTs. ITTs, an indicator of tissue insulin sensitivity, were performed in two of the three papers, and this included only male mice that were wild type, or floxed mice with either normal or localised adipose specific AhR deficiency. The pooled mean differences between vehicle and PCB treatment are shown in Fig. 6. Overall mean AUC in ITTs was not different between vehicle and CB77 treated animals (standardised mean difference = -1.54 [-3.25, 0.16]) such that they did not differ in responsiveness to insulin. Inspection of the Forest plot shows that lower AUC in vehicle compared to CB77 treated animal was only seen in mice with intact AhR. Effect sizes for AUC in the ITT tests ranged from 0.99 to 2.28 and the direction of effect was consistent across all animal models. Heterogeneity was low and did not differ between animal models ($I^2 = 0$; $\tau^2 = 0$; $Q = 1.83$; $p = 0.401$).

3.4.3. Excluded studies

Nineteen papers that reported on intentional weight loss and contaminant exposure in animals set out to understand how chemicals are redistributed during weight loss (7) and/or investigated the impact of chemical exposure on another aspect of physiology (12), and in each case measured mass loss as part of the study. However, mass loss or glycemic control was not the main outcome of interest. Although relevant data exist from these studies, they could not be extracted because they were typically presented as group averages and did not pair the contaminant values with mass per individual. The range of chemicals examined included the organophosphate pesticide, parathion; chlorinated and brominated POPs; copper, zinc and cadmium; with no studies on fluorinated compounds or plasticisers and these studies represented a wider range of farmed and laboratory species as well as wildlife. Characteristics of these studies including chemical of interest, diet intervention and outcomes measured are provided in OSF (DOI <https://doi.org/10.17605/OSF.IO/N5R8S>).

Several of these studies provided some information on mass change trajectories during weight loss during and/or after exposure to a variety of chemicals. Of the seven studies that examined redistribution and elimination five reported that the chemical of interest, in each case an OCP, did not slow weight loss. One suggested impaired weight gain during *ad libitum* feeding and or increased weight loss during food restriction in higher dose groups [52] and the remainder reported no chemical effect. Nevertheless, in many cases, data and details of the statistics reported in text were not provided. Two of these seven papers [53,54] did not examine effects of the chemical, in this case heptachlor and PCB, on mass loss. In the remaining 12 studies examining impacts of chemical exposure during dietary weight loss on other aspects of physiology, ten, primarily on chlorinated compounds, but also including one study on cadmium, found no effect of the chemical or mixture on weight loss trajectory [55–63], one in rats and exploring DDT, showed an increase in mass loss in exposed versus unexposed animals subjected to diet restriction [64], similar to [49] and only one, on HCB in rats, showed that the rate of mass loss was slower in exposed versus unexposed groups [65].

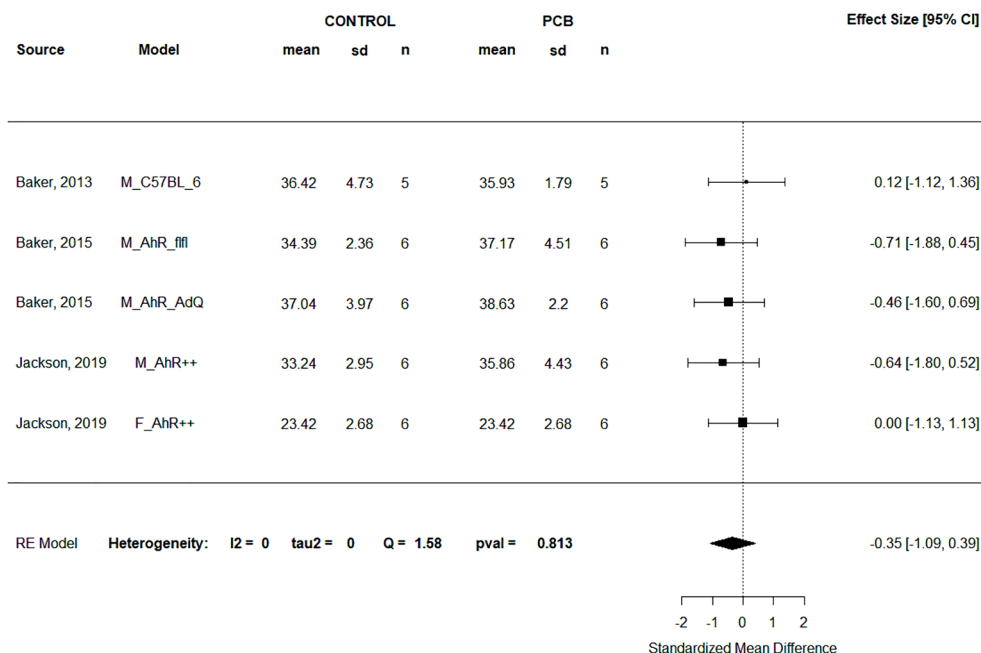


Fig. 4. Standardised mean differences and confidence intervals between control and CB77 treated mice in final mass after a 4 week calorie restricted diet. The paper from which the data were extracted is shown on the left, followed by the sex (M or F) and genetic model, then mean, standard deviation and n for each group. The box size for each animal model reflects sample size. Effect size and 95 % confidence intervals are given on the right. Aggregated effect size for each study was calculated by fitting a three-level meta-analysis. The diamond beneath shows the pooled mean difference and the dashed vertical line indicates parity between groups. Heterogeneity between studies (I^2 ; τ^2 and Q) is indicated beneath the Forest plot.

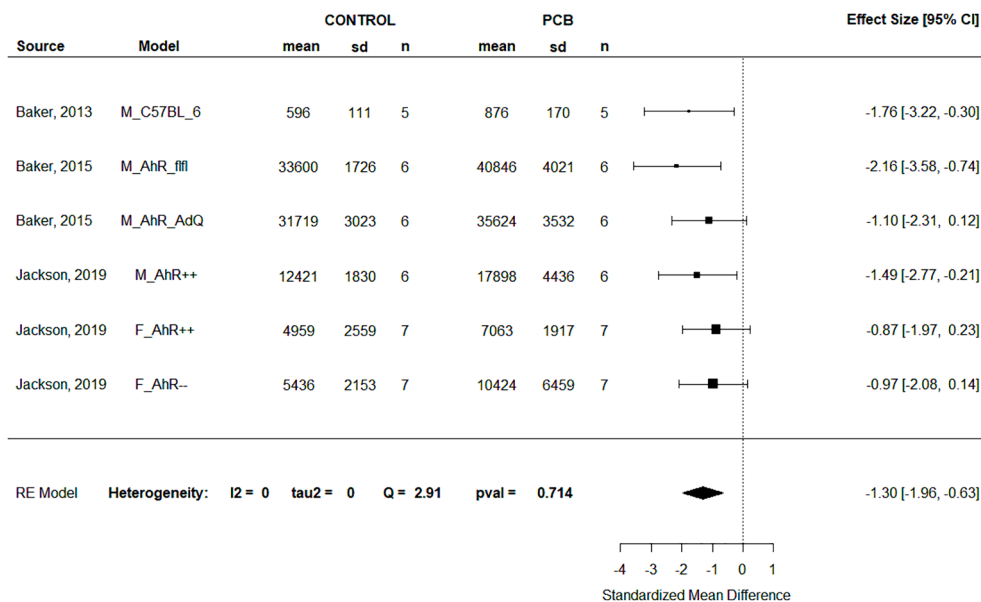


Fig. 5. Standardised mean differences and confidence intervals between control and CB77 treated mice in AUC in GTT tests after a 4 week calorie restricted diet. The paper from which the data were extracted is shown on the left, followed by the sex (M or F) and genetic model, then mean, standard deviation and n for each group. The box size for each animal model reflects sample size. Effect size and 95 % confidence intervals are given on the right. Aggregated effect size for each study was calculated by fitting a three-level meta-analysis. The diamond beneath shows the pooled mean difference and the dashed vertical line indicates parity between groups. Heterogeneity between studies (I²; tau and Q) is indicated beneath the Forest plot.

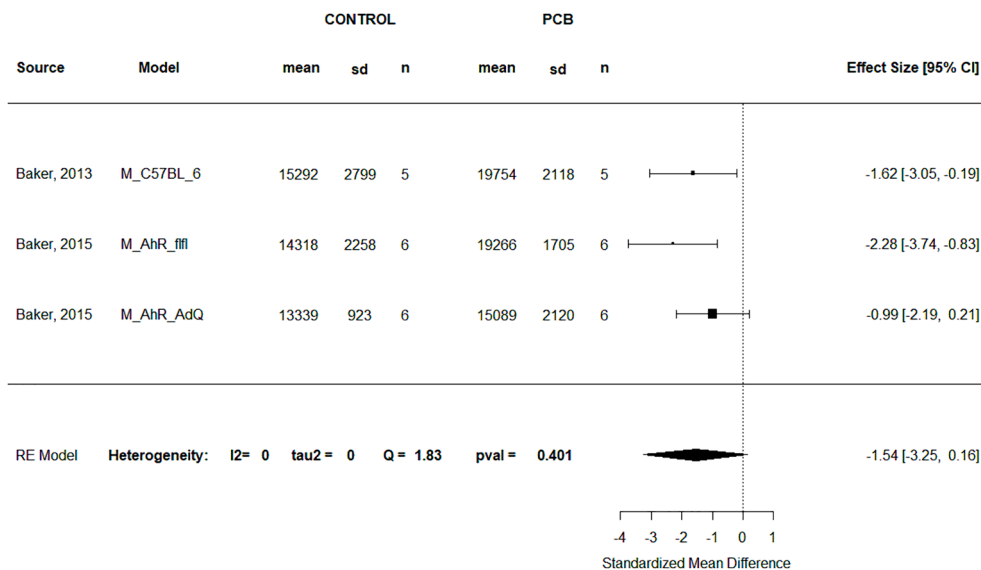


Fig. 6. Standardised mean differences and confidence intervals between control and CB77 treated mice in AUC in ITT tests after a 4 week calorie restricted diet. The paper from which the data were extracted is shown on the left, followed by the sex (M or F) and genetic model, then mean, standard deviation and n for each group. The box size for each animal model reflects sample size. Effect size and 95 % confidence intervals are given on the right. Aggregated effect size for each study was calculated by fitting a three-level meta-analysis. The diamond beneath shows the pooled mean difference and the dashed vertical line indicates parity between groups. Heterogeneity between studies (I²; tau and Q) is indicated beneath the Forest plot.

4. Discussion

A small number of preclinical animal studies over the last ten years have addressed the hypothesis that exposure to environmental contaminants can alter body mass loss and glycemic control during deliberate calorie restricted weight loss. These studies suggest persistent legacy and emerging chemicals of concern can prevent the benefits of calorie restriction to metabolic health.

4.1. Evidence for chemical effects on mass loss during calorie restriction

Humans enrolled in trials can deviate from the prescribed diet and may either drop out or fail to comply. If contaminants affect appetite they may influence mass loss rates by changing eating behaviour and impact on compliance. Animal studies differ from ‘real-life’ human experience because the animals cannot respond to impacts on their appetite when food is restricted. The preclinical data is thus important because it removes the potential for confounding effects on eating behaviour. The data from these studies should thus allow the detection

of effects on mass loss, if one exists, independent of appetite alterations and this is a major strength of such preclinical studies. However, current evidence is limited.

Only one of the studies provided evidence for chemical effects on body mass loss trajectories during calorie restriction, and this showed greater body mass loss in DDT treated animals compared to controls [49]. One human study [66] showed blood DDE levels, along with other POPs, increased during body mass loss in humans and linked this increase in circulating POPs to subsequent alteration of glycemic control but not with any change in body mass loss rate. The dose in the rat study reflected DDT levels in crude salmon oil, which humans only experience if they eat fresh caught fish from contaminated areas regularly. The doses in the rats may thus have been higher than in the human study [66] and perhaps higher than other typical human exposures, but lack of reporting on the blood levels of DDT in the rats mean it is not possible to compare with human studies.

PFOS and PCBs had no direct impacts on the weight loss achieved by calorific restriction in the rodent studies here, similar to human studies [66–68]. However, the animal studies were likely to be underpowered in terms of ability to detect small but important differences in final body mass between control and chemical exposed groups. Only one study performed a power analysis [18]. Greater sample sizes would be needed to detect a 10 % body mass difference between control and intervention groups. Clinically relevant weight loss in humans is around 5–10 % body mass, thus preclinical studies would have to produce this body weight change in controls over a 6–8 week time period and the sample size required for such an experiment in rats or mice is unclear from the data available. The 4-week calorie restriction in [13] elicited 7.9 % mass loss in vehicle treated and 8.2 % mass loss in CB77 treated animals, but was not extractable for the other PCB studies. The 25 % calorie restriction for 6 weeks in the PFOS study in mice [18] also produced only ~ 5 % body mass loss and the animals were not provided with a HFD to gain mass prior to calorie restriction, such that the dietary conditions in this study did not reflect the typical weight gain that occurs in humans prior to managed weight loss programmes. Although the aim in Ishikawa et al was to mimic the 20–25 % body mass loss seen in bariatric surgery [49], the calorie restriction produced a 5–10 % mass loss compared to maximum mass at the end of the HFD phase, and returned mass to broadly the same level as prior to the HFD. Either duration or degree of calorie restriction would need to be more extreme to produce a body mass loss in mice comparable to those that are clinically effective in improving glycemic control in humans. In other mouse studies, 40–60 % kcal deficits have been used [69,70] and may be more appropriate for translational study design, but may be more difficult to achieve in female animals, which are smaller. An additional consideration is that final body mass measures rather than fat mass loss rate may be relatively insensitive to contaminant effects on metabolism. The preclinical data is thus limited in its support for chemical exposure influencing weight management, but improved study designs could help determine whether impaired weight loss is a consequence of exposure.

4.2. Evidence for chemical effects on glycemic control

The animal studies do provide evidence for altered liver function and fat accumulation, and glucose homeostasis in response to persistent bioaccumulative contaminants, even at more conservative body mass reduction than those used in human clinical trials required for favourable glycemic and cardiovascular outcomes. Both PCB and PFOS decoupled body mass loss from its expected benefits on glucose control, and this, rather than altered body mass loss alone, is therefore an important aspect to include in clinical studies. Glycemia was not explored in the rat study [49]. This is surprising given that this group's previous results showed that crude salmon oil exposure led to greater insulin resistance than in controls fed refined oil or corn oil [51]. We can find no evidence of a follow up study exploring whether insulin resistance induced by HFD and worsened by POP exposure is also slower to

resolve.

The animal studies on CB77 are consistent with the observation of altered blood glucose control accompanying PCB release during weight loss in humans [66,67]. The greater effects observed in male mice on glucose homeostasis reflect the observation that PCB release during weight loss is associated with altered glucose control in men, not women [66]. However, the findings are not entirely concordant. One human study shows an association between increased PCBs in the blood stream during weight loss and lower fasting insulin levels in men [66] and another shows a greater drop in both fasting glucose and HbA1c, but a muted increase in β -cell function in people with T2DM [67]. The animal studies provide reason to believe there is a plausible causal link between exposure and impaired glycemic control at biologically realistic PCB doses that requires further investigation in dedicated clinical studies. Indeed, other experimental mouse work shows that PCB exposure can alter pancreatic function, insulin sensitivity and liver steatosis [71–73].

The findings from [18] align with human studies that suggest PFOS can lower metabolic rate, but not mass change, in humans during weight loss diets [68,74] and may alter other aspects of metabolic health. The human studies suggest resting metabolic rate is reduced by PFOS, and the animal study identifies altered liver function, hepatic lipid accumulation and glucose regulation after weight loss as consequences of PFOS exposure prior to the calorie restriction. However, the reciprocal studies have not been performed. The animal data suggest that liver fat content may be an informative outcome to measure in clinical research examining effects of PFAS on weight loss and its associated health outcomes.

The lack of preclinical data on other chemical groups highlighted here prevents conclusions about the impact of other types of chemicals on weight loss and beneficial effects on glucose control, particularly those that have been identified as potentially problematic for human metabolism in clinical research, such as phthalates and parabens [75]. In general, the preclinical studies postdate the original sample collection in human studies performed in the early 2000 s or 2010–2013. This highlights issues identified previously that preclinical studies are underused [29] and could be better deployed to inform human studies on the likely most problematic chemicals that impair weight management of individuals with T2DM and obesity. We make recommendations for how this may be achieved in Table 6.

4.3. Evidence weaknesses

4.3.1. Diet

While animal studies involving diet restriction can isolate the purely metabolic effects of chemical exposure, and this can be a strength of the study design, any effects that such chemicals may have on appetite or motivation are masked because choice is removed. This aspect of potential chemical impact on weight management thus requires further exploration. In addition, the HFD regimes used here are standard approaches to enhance fat mass and generate insulin resistance, but do not normally generate T2DM in this strain. For example, in mouse studies on the same strain, animals may have high fasting glucose, elevated cholesterol and C-peptide after 6–8 weeks, but usually require 16–20 weeks to develop other characteristics of T2DM [76], and this typically models insulin resistance but does not involve pancreatic impairment. The HFD durations used here thus may represent early stages of some aspects of prediabetes but do not reflect the full expression of T2DM in humans in either its early or established stages. In the rat study, the animals selected were already prone to develop obesity, such that the additional weight gain during the HFD phase was modest and the calorie restriction simply returned them to their pre HFD weight. The animal studies here thus do not represent all the ways in which chemical exposure could impact weight loss in humans or how chemical exposure may impact weight loss and glycemic control, particularly in emerging or established T2DM.

4.3.2. Age and sex

As highlighted elsewhere [77] the rodent studies here exclusively used males, perhaps because the metabolic phenotype is typically more severe [78]. In contrast, the human studies on contaminant effects on weight loss and/ or glucose control consistently recruit many more women than men. In addition to reported sex differences in T2DM and extreme obesity risk, clinical studies do often show sex differences in the apparent response to chemical exposure. For example, in one human study, the association between altered insulin levels and PCB release during weight loss was apparent in men and not women [66]. Conversely, PFAS seemed to impact women's weight regain more strongly than in men [68]. Preclinical studies should always include sex differences, and this is typically now mandated by funders, but may not have been required when these studies were performed. Sex differences in vulnerability of metabolic health markers and changes with age remain to be robustly explored.

Animal studies also generally used young animals and short duration chemical exposures. Most humans do not encounter high doses of any individual chemical in a specific time window but are exposed in a continuous or pulsatile way to chronic low doses throughout their lifetime. In addition, clinical trials and health care intervention programmes, such as those offered by the National Health Service (NHS), typically recruit older participants, such that the rodents are not of a representative age to extrapolate findings to human outcomes. To better reflect human exposures and the demographics on which clinical trials of weight loss effectiveness for T2DM management are initiated, animal studies need to examine impacts of lifelong low dose exposures with calorie restriction initiated later in life.

4.3.3. Exposure dose, duration and route

Timing of exposure is a key consideration in preclinical studies. In the studies on CB77 and DDT, exposure was discontinued during weight loss, whereas in the PFOS study, exposure began simultaneously with calorie restriction and animals had been able to gain weight without accumulating the chemical during high fat feeding. In humans, unintentional exposure will likely always accompany weight gain and precede any weight loss attempts, thus the PFOS exposure regime in [18] is not the most appropriate to model the dynamics in human weight gain and loss. If provided with a complete diet replacement, PCB dietary exposure may drop dramatically in human participants, making the exposures in the preclinical studies on CB77 more reflective of exposure patterns during such study design. In both humans and rodents, weight

loss causes a large increase in circulating POPs as they are mobilised along with fat [66]. Exposure to specific chemical groups through diet may not cease or decrease very dramatically if weight loss occurs during unsupervised calorie restricted diets and food sources do not change. Understanding the dynamics of chemical exposure changes in humans during different means of weight loss and ensuring that the preclinical studies reflect the same exposure patterns and dynamics will be key in ensuring such studies maximise their translational benefit.

Humans are also exposed chronically to a cocktail of chemicals at low doses that may interact synergistically or competitively. While preclinical studies that target a single chemical may be important in distinguishing mechanisms of action, toxic effects of individual compounds, and in providing proof of concept of a particular chemical effect, they do not reflect the typical complex chemical exposures experienced by humans. Some excluded studies used contaminated food [56,61], extracts from contaminated prey items [57] or chemical mixtures based on typical exposures in human 'shopping basket' studies [79] in wild, farmed or laboratory animals. These approaches are more biologically realistic even if they do not identify the individual compounds responsible for observed biological effects. Preclinical studies that use contaminants from food extracts or use exposure cocktails derived from either published exposure estimates or studies in which human impacts have been observed are urgently needed to better understand the real threats posed by such chemical combinations to human metabolic health.

Dosage route also needs to be considered. In the studies described here gavage was used to administer the chemical, such that animals received a bolus at multi-day, weekly or multi-week intervals. This may be a convenient way to deliver the chemical, to ensure the animal receives the full intended dose, and reflects exposure through ingestion, but humans do not experience POP exposure in this highly pulsatile way, which could produce unintended acute effects such as altering the gut microbiome. Animal studies thus need to include transplacental, and breastmilk routes of exposure as well as delivery through food and or water after weaning to better mimic the dynamics of PCB and PFAS accumulation in fat and its presence in the blood stream. While a range of studies use these routes of exposure to examine other questions, and more commonly in wildlife or farmed species, they have not thus far incorporated a weight loss component and with an appropriate unexposed control group or measured outcomes related to glucose control and body fat content.

Table 6

recommendations for future work exploring effect of contaminants on weight loss trajectory or glycaemic control during weight-loss diet interventions.

Aspect	Recommendation
Study design	Ensure exposure precedes intentional weight loss Provide clarity on why and how animals are chosen for specific measurements when a subgroup are used Ensure randomisation and appropriate blinding in husbandry as well as experimental measures Use PREPARE guidelines [86]
Animal characteristics	Include females and a wider range of genetic backgrounds of laboratory animals Include animal models of T2DM and impaired glucose tolerance (IGT) Include older animals that have experienced chronic exposure to better model later onset disease
Diet	Ensure target of minimum 5 % mass loss and aim for 10 % sustained weight loss to observe biologically meaningful change and to ensure glycaemia improvement in 'positive control' animals and to mimic successful mass loss in humans.
Chemicals of interest	Ensure chemical levels in blood or other target tissue (adipose/ liver) are representative of the levels found in human populations at concentrations associated with T2DM or obesity New studies that reflect current exposures of a range of candidate contaminants Use exposure routes and timeframes that reflect typical dietary (or other) exposure for humans since gavage produced artificial pulses in exposure Include transplacental, and breastmilk routes of exposure Use chemical cocktail exposures that better represent real world exposures
Outcomes	Include wider range of more sensitive and biologically meaningful outcomes than just mass. Absolute body fat and visceral fat content as well as resting metabolic rate, liver fat content, cholesterol, or inflammation markers Include glycaemia control metrics including HOMA-IR/ β , GTT and/or HbA1c.
Analysis and reporting	Ensure per treatment reporting, including completion data and ensuring clear comparison of contaminant levels at baseline between completers and non-completers if relevant. Adhere to ARRIVE guidelines in reporting and provide checklists [87,98]. Provide data to allow extraction, such as in data repository in addition to summaries in papers. Clear reporting of statistics Journals require ARRIVE checklist and editors/ reviewers required to check items [87,90]

4.3.4. Animal model

The mouse studies here largely used C57BL/6 mice which is typical of biomedical studies [80] perhaps because they produce maximal expression of mutations (<https://www.jax.org/strain/000664>), which was useful for the studies that used knock outs and knock-downs of AhR. One striking finding from the mouse work was the importance of AhR and its influence on the rate of PCB and other POP elimination during weight loss. This may be a major influence on the extent to which individuals respond to these chemicals and how well they resume glycaemic control. A human study stratifying by AhR genotype may be a rapid and clinically illuminating approach to establish the impact of these chemicals on weight and glucose control.

C57BL/6 mice tend to develop obesity and/or obesity induced hyperglycemia [81], but it is controversial whether the animals developed overt T2DM in these studies [76]. The different substrains of C57BL/6 mice differ in their metabolic phenotype [80], which could impact the representativeness and applicability of the findings. Irrespective of the precise genetic background the use of only one inbred animal strain makes it difficult to generalise from the limited studies available on CB77 and PFOS. Charles River strain of Sprague Dawley rats was chosen because it exhibits rapid weight gain [49]. This strain has increased visceral adiposity even by one month of age, shows impaired insulin sensitivity and altered glucose and lipid metabolism by 3 months, and increased free fatty acids and skeletal muscle triglyceride content as adults at six months compared to the lean Harlan strain, even on the same food intake [82]. Studies on the benefits of calorie restriction for longevity show enormous differences between model strains and species [83], and such genetic and species differences may impact on the responses to chemical exposure in conjunction with calorie restriction. Indeed, recent evidence in humans suggests that genetic risk scores for lipodystrophy may modify the risk of T2DM from organochlorine pesticides [84]. While use of inbred strains is recommended within studies to minimise between animal differences, use of other species and strains that differ in their tendency to develop these metabolic disorders [85] are needed to explore the reproducibility of the findings across genetic backgrounds and models and ensure translational relevance.

4.3.5. Reporting

Issues with confidence in reporting of results and analysis are likely to be improved with greater use of Planning Research and Experimental Procedures on Animals: Recommendations for Excellence (PREPARE) [86] and Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines [87,88] and open research pipelines such as protocol pre-registration and data sharing. Nevertheless, recent work has highlighted the limited requirement for, and reporting of, basic information required in the ARRIVE checklist in animal experimental studies [89], even when required at submission [90]. Reviewers and editors would benefit from clearer instructions and requirements to check against such guidelines, and this needs to become common practice to improve confidence in preclinical results.

There were very low numbers of papers that addressed the hypothesis of interest. However, a larger number of papers on animals (19) included body mass loss as an outcome in studies intended to explore redistribution or another aspect of chemical impact on physiology and these papers often referred to testing for the effect of the chemical on mass loss during food restriction. These papers were excluded here because they did not address our question of interest directly or reported in a way that did not allow the data to be extracted. That said, most indicated no effect of the chemicals of interest, with a small number indicating higher mass loss or fat loss in exposed versus control groups. Caution needs to be exercised in inference from these studies because sample sizes were often small, chemical doses were often high to examine toxicological effects rather than those that reflect low dietary exposure; diet interventions were short and severe and/or exposure was administered after the onset of the low-calorie treatments rather than prior to weight loss. Nevertheless, information from these studies shows

the breadth of chemical groups and species on which toxicological studies are often performed from which data could be used in post hoc analysis to examine chemical exposure effects on diet induced weight loss or improvements to glycaemic control. More complete reporting may allow clear identification of null results if studies are appropriately powered and thus help to focus attention on more problematic chemicals. Modern requirements for data deposition may allow studies in which weight loss and other relevant parameters on glycaemic control and body fat content were measured to be analysed from publicly available datasets if information is presented per animal or effect size per treatment group.

4.4. Study weaknesses

It is possible that there are many more toxicological studies that meet our criteria in terms of data on weight loss rates during food restriction, but that were not identified by the search because they did not aim to explore weight loss *per se* but examined elimination and distribution. Such papers are difficult to identify using specific search terms and have serious weaknesses as discussed above but may reveal more evidence of null results. We may also have missed other studies on glycaemic control because our search did not include such terms. Nevertheless, a sensitivity analysis of searches that included the terms insulin, glucose, insulin resistance, insulin sensitivity, homeostatic model assessment, glucose tolerance test, insulin tolerance test and GTT, ITT and HOMA did not identify additional relevant hits, such that we are confident we have comprehensively examined the existing literature with the current search terms.

We did not explore chemical groups that have either been associated with other human health risks, including benzophenones, acrylamide, mycotoxins such as deoxynivalenol, and organophosphorus flame retardants [91,92], or associated with plastics, such as phthalate substitutes including 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH), its monoester, cyclohexane-1,2-dicarboxylic monoisononyl ester (MINCH) [93], tris (2-ethylhexyl) trimellitate (TOTM) and acetyl tributyl citrate (ATBC), recently identified as a potential obesogen [94], because these substances have not yet been linked with T2DM in the human literature and obesogenic effects are equivocal [95]. Omission of such search terms may miss out some studies but given that the clinical and preclinical research is so sparse it seems unlikely that such chemical groups have yet been considered in the context of impacts on weight loss and glucose control during a calorie restricted diet.

Our data extraction was limited by use of digitisation from graphs, including ambiguity over individual points and what animals are presented as well as accuracy over assigning points. We attempted to be conservative in our data extraction and performed dual extraction and thus believe data extraction reflects the best estimates from publicly available information from these studies.

4.5. Study strengths

Our study sought to explore a wide range of chemicals to ensure broad coverage of pollutants that have been identified as potential risks for obesity and T2DM development even when that risk has not been replicated across multiple epidemiological studies. The SYRCLE tool to assess risk of bias is published [36] and the context specific signal questions can be used by others to ensure our approach is reproducible and comparable to other animal study systematic reviews. Rigorous accounting for the clustering of experiments within papers allowed us to derive a conservative pooled effect size for CB77 and minimise over interpretation of data available.

4.6. Conclusion

Our study highlights the paucity of preclinical data on the effects of contaminant exposure on weight loss and glycaemic control resulting

from calorie restriction. The limited evidence available tends to support the sparse human data suggesting PFOS can reduce metabolic rate and thus facilitate weight regain after a dietary weight loss, and that PCBs may alter glucose control. However, the evidence is currently inadequate to draw firm conclusions. There is a complete lack of information on other widespread chemicals and on their mixtures, which emphasises the limited use made of preclinical studies to inform human clinical interventions. We suggest three main areas where significant improvement is needed in preclinical study design:

1. More systematic examination of PCBs, PFOS, other chemical groups implicated in T2DM and obesity development, and in realistic combinations, doses and routes of exposure.
2. Studies must investigate potential sex differences and focus on animals which have been exposed to chemicals at lower doses, chronically, over a significant portion of their lifetime.
3. A more varied use of models of metabolic disease and genetic variation is required to improve translation of findings to the human population.

Wider use and more careful design and reporting of preclinical studies will also allow clinical work to ensure samples from human studies are used most appropriately to maximise our understanding of the role of chemicals in impairing diet-induced weight loss and its metabolic benefits. Preclinical studies must inform, focus and improve clinical study design. Ultimately the goal is to determine whether screening for chemical exposure prior to use of weight loss interventions would improve clinical outcomes, personalise diabetes management and focus healthcare resources on those who would benefit the most.

Ethics approval

This study is a systematic review of data already anonymised and available in the public domain. Expedited approval has been granted for this work by the Abertay University ethics committee (reference EMIS 5911).

CRediT authorship contribution statement

K.A. Bennett: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **C. Sutherland:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology. **A.L. Savage:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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