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Organochlorine Pesticide Exposure Induces Insulin Resistance and Metabolic Disruption in Laboratory Animal Models: A Review of Mechanisms and Evidence

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Abstract:
Insulin resistance and its downstream metabolic sequelae, including type 2 diabetes and obesity, have risen in parallel with widespread environmental contamination by persistent organic pollutants. Among these, organochlorine pesticides (OCPs) such as dichlorodiphenyltrichloroethane (DDT) and its metabolite DDE, chlordane, dieldrin, and hexachlorobenzene remain detectable in soil, water, and adipose tissue decades after regulatory restriction, owing to their lipophilicity and resistance to degradation. This review synthesises evidence from laboratory animal and cell-based models demonstrating that OCP exposure disrupts glucose homeostasis through multiple, interacting mechanisms: aryl hydrocarbon receptor activation and interference with PPARγ-dependent adipogenesis, oxidative stress and serine phosphorylation of insulin receptor substrate-1, mitochondrial electron transport chain inhibition, adipose tissue remodelling with macrophage infiltration, low-grade systemic inflammation, pancreatic beta-cell secretory dysfunction, and gut microbiota disruption. Rodent studies exposed to environmentally relevant organochlorine mixtures consistently show impaired whole-body insulin sensitivity, visceral adiposity, and hepatic steatosis, while in vitro beta-cell models reveal direct impairment of insulin synthesis and secretion. Collectively, the evidence supports a causal, mechanistically plausible role for organochlorine pesticide exposure in the aetiology of insulin resistance, independent of dietary energy balance. The review highlights persisting gaps concerning mixture effects, dose-response thresholds at environmentally realistic exposure levels, and sex-specific vulnerability, and underscores the continued public health relevance of legacy pesticide residues.

Keywords: organochlorine pesticides; insulin resistance; metabolic disruption; animal models; endocrine disruption; oxidative stress; adipose tissue; type 2 diabetes.

1. Introduction

The global prevalence of insulin resistance, metabolic syndrome, and type 2 diabetes has continued to climb even as public health efforts have targeted diet and physical inactivity, prompting closer scientific attention to environmental contributors that operate independently of energy balance. Organochlorine

pesticides (OCPs), a class of chlorinated hydrocarbons that includes DDT and its persistent metabolite DDE, chlordane, dieldrin, aldrin, heptachlor, lindane, and hexachlorobenzene, were used extensively in agriculture and vector control through the mid-twentieth century. Although most OCPs have been banned or severely restricted since the 1970s and 1980s under national legislation and, subsequently, the Stockholm Convention on Persistent Organic Pollutants, their chemical stability and high lipid solubility mean that residues persist in soil, sediment, the food chain, and human and animal adipose tissue to the present day.

Epidemiological research has repeatedly associated body burdens of organochlorine compounds with elevated risk of type 2 diabetes, dyslipidaemia, and insulin resistance, even at low, background exposure concentrations. Cross-sectional analysis of the National Health and Nutrition Examination Survey found a strong, graded relationship between serum concentrations of several persistent organic pollutants, including organochlorine pesticides, and the prevalence of diabetes, with risk rising sharply across quintiles of exposure even after adjustment for obesity (Lee et al., 2006). A subsequent nested case-control study extended this finding prospectively, showing that low background concentrations of specific organochlorine pesticides measured years in advance predicted incident type 2 diabetes (Lee et al., 2010). Related work in a large prospective cohort found that several organochlorine pesticides predicted higher body mass index, triglycerides, and insulin resistance as measured by the homeostasis model assessment, with associations following an inverted U-shaped, rather than strictly linear, dose-response curve in which effects were most pronounced at low-to-moderate exposure levels (Lee et al., 2011). Comparable associations between organochlorine and related pollutant burden and impaired glucose tolerance have also been reported outside industrialised dietary contexts, including among Greenland Inuit populations with high traditional consumption of marine fat (Jørgensen et al., 2008), and in the general United States population using dioxin, PCB, and DDT biomarkers (Everett et al., 2007).

Taken together, this epidemiological literature establishes a consistent, dose-related statistical association between organochlorine body burden and impaired glucose homeostasis across diverse human populations. However, observational human studies cannot, by themselves, establish causality, rule out reverse causation (whereby adiposity itself increases pollutant body burden through lipophilic partitioning), or elucidate the molecular pathways involved. Laboratory animal models—rodent feeding studies, in vitro adipocyte and pancreatic beta-cell systems, and aquatic model organisms—have therefore played a central role in testing whether organochlorine exposure directly produces insulin resistance under controlled conditions and in dissecting the mechanisms responsible. This review synthesises the experimental animal and cell-based literature on organochlorine pesticide exposure and metabolic disruption, with particular attention to the molecular pathways connecting exposure to impaired glucose homeostasis, and considers how this experimental evidence base corroborates and extends the human biomonitoring findings summarised above.

The review draws on peer-reviewed rodent feeding studies, aquatic model organism studies, and in vitro adipocyte and pancreatic beta-cell experiments identified through the toxicological and endocrinology literature on organochlorine pesticides and structurally related persistent organic pollutants, with priority given to studies using exposure concentrations and routes intended to approximate environmentally or dietarily realistic conditions rather than acute high-dose toxicology protocols. Studies using purely acute, high-dose lethality or carcinogenicity endpoints, which address a different toxicological question, are outside the present scope. The remainder of the review is organised as follows: Section 2 outlines the chemical properties underlying organochlorine persistence; Section 3 details the principal molecular

mechanisms by which these compounds are proposed to disrupt insulin action; Section 4 reviews specific experimental animal and cell-based studies and relates their findings to the parallel human biomonitoring literature; and Sections 5 through 7 discuss the broader implications, limitations, and conclusions arising from this body of evidence.

2. Organochlorine Pesticides: Classification and Environmental Persistence

Organochlorine pesticides share a common structural feature of multiple chlorine substitutions on an aromatic or cyclodiene backbone, which confers chemical stability, resistance to microbial and photolytic degradation, and pronounced lipophilicity. This last property allows OCPs to bioaccumulate in fatty tissue and biomagnify along the food chain, so that organisms at higher trophic levels—including humans and many laboratory or companion animal species—carry disproportionately high body burdens relative to ambient environmental concentrations. Commonly studied compounds include DDT and its principal metabolite p,p′-DDE, the cyclodienes (chlordane, dieldrin, aldrin, heptachlor, endosulfan), hexachlorocyclohexane isomers (including lindane), and hexachlorobenzene. Structurally related polychlorinated biphenyls (PCBs) and dioxin-like compounds are frequently studied alongside OCPs because they co-occur in environmental and dietary matrices and are often grouped together under the broader category of persistent organic pollutants (POPs).

Half-lives for individual organochlorine compounds in soil and in animal or human adipose tissue range from several months to multiple decades, meaning that populations and experimental animals alike may carry measurable residues long after direct exposure has ceased. Dietary intake, particularly of fatty fish, dairy, and animal fats, remains the principal ongoing route of exposure for both humans and many laboratory animal colonies fed standard chow, a consideration that has itself influenced the design of several of the feeding studies discussed below.

Because standard laboratory rodent diets are typically formulated from plant- and marine-derived fats and fish meal, animal facilities are not exposure-free environments by default; background organochlorine and PCB contamination of standard chow has been documented and represents a potential confound that well-designed studies must explicitly control for, typically by comparing purified or contaminant-depleted diets against diets deliberately fortified with environmentally realistic organochlorine mixtures. This design logic underlies the refined-versus-crude fish oil comparison used by Ruzzin et al. (2010) and is central to interpreting the causal claims of the animal literature reviewed in Section 4.

The physicochemical properties that make organochlorine pesticides effective, long-lasting agricultural and vector-control agents are the same properties that underlie their toxicological persistence and bioaccumulation potential. High octanol-water partition coefficients favour storage in triglyceride-rich adipose tissue over excretion, while chlorine substitution confers resistance to the oxidative and hydrolytic enzymes that typically degrade organic molecules in soil, water, and hepatic tissue. As a consequence, mobilisation of stored organochlorine compounds from adipose tissue—during weight loss, lactation, fasting, or advancing age-related fat redistribution—can transiently elevate circulating concentrations and target-organ exposure even in the complete absence of new environmental intake, a phenomenon that has itself been proposed as a mechanism connecting weight loss interventions to paradoxical short-term deteriorations in insulin sensitivity in both animal models and human studies of legacy pollutant burden.

3. Mechanisms Linking Organochlorine Exposure to Insulin Resistance

Experimental work over the past two decades has identified several, frequently overlapping, molecular pathways by which organochlorine pesticides disrupt insulin signalling and glucose homeostasis. These pathways are summarised in Table 2 and elaborated below.

3.1 Receptor-Mediated Endocrine Disruption

Many organochlorine compounds act as ligands for the aryl hydrocarbon receptor (AhR), a transcription factor that, when activated, cross-talks with metabolic regulatory pathways including peroxisome proliferator-activated receptor-γ (PPARγ), the master regulator of adipocyte differentiation and insulin sensitivity. Interference with PPARγ-dependent gene expression alters the balance between healthy, insulin-sensitive adipogenesis and the accumulation of dysfunctional, hypertrophic adipocytes. In the rat feeding study conducted by Ruzzin et al. (2010), exposure to a POP mixture dominated by organochlorine pesticides down-regulated insulin-induced gene-1 (Insig-1) and Lpin1, two genes central to lipid homeostasis, in both whole adipose tissue and cultured adipocytes, directly linking receptor-level disruption to impaired lipid partitioning and insulin action.

3.2 Oxidative Stress and Impaired Insulin Signalling

A substantial body of evidence implicates oxidative stress as a convergent mechanism underlying insulin resistance induced by diverse toxicant classes, including organochlorine pesticides. Reactive oxygen species (ROS) generated in response to organochlorine metabolism promote serine, rather than tyrosine, phosphorylation of insulin receptor substrate-1 (IRS-1), which uncouples IRS-1 from downstream phosphatidylinositol 3-kinase/Akt signalling and impairs GLUT4 translocation to the plasma membrane, thereby reducing insulin-stimulated glucose uptake in adipocytes and myocytes. Computational and experimental modelling of insulin signalling in rodent adipocytes has shown that while transient, moderate oxidative stress can acutely potentiate glucose transport, sustained oxidative stress instead degrades IRS-1 and the transcription factor FOXO, producing a net impairment of insulin action consistent with the pattern observed following chronic organochlorine exposure (Smith & Shanley, 2013).

3.3 Mitochondrial Dysfunction

Several organochlorine and related persistent organic pollutants accumulate within mitochondrial membranes owing to their lipophilicity, where they can inhibit electron transport chain complexes and reduce oxidative phosphorylation efficiency. The resulting decline in ATP generation, combined with increased mitochondrial ROS leakage, impairs the substantial energetic demands of insulin-responsive tissues such as skeletal muscle and liver, and has been proposed as a unifying mechanism connecting persistent pollutant body burden to the broader metabolic syndrome phenotype. Aquatic model organisms exposed to graded, environmentally realistic mixtures of organochlorine pesticides have shown altered hepatic mitochondrial complex I–IV activity alongside disturbances in glucose, insulin, free fatty acid, and triglyceride levels, with integrated metabolomic, proteomic, and transcriptomic profiling pointing to a mitochondrial route to type 2 diabetes-like dysregulation that complements the rodent findings described in Section 4.

3.4 Adipose Tissue Remodelling and Inflammation

Organochlorine compounds preferentially partition into adipose tissue, where they appear to promote a pro-inflammatory, insulin-resistant adipocyte phenotype. In the mouse study by Ibrahim et al. (2011), animals fed a diet incorporating POP-containing farmed salmon developed expansion of epididymal, retroperitoneal, and inguinal fat pads together with infiltration of F4/80-positive macrophages into adipose tissue, a histological hallmark of adipose inflammation that parallels findings in diet-induced obesity

models. Macrophage infiltration is associated with local secretion of tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which activate the c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) pathways in adjacent adipocytes and hepatocytes, further impairing IRS-1 function and compounding insulin resistance initiated by direct receptor- and oxidative stress-mediated mechanisms. This inflammatory adipose phenotype also alters the secretory profile of adipokines such as adiponectin and leptin, which under normal conditions help coordinate whole-body insulin sensitivity, so that organochlorine-driven adipose dysfunction may propagate insulin resistance to the liver and skeletal muscle even in animals that do not show large increases in total body fat mass.

3.5 Pancreatic Beta-Cell Dysfunction

Beyond peripheral insulin resistance, organochlorine compounds appear capable of directly impairing pancreatic beta-cell function. In vitro studies exposing murine and human pancreatic beta-cell lines to sub-lethal concentrations of p,p′-DDT and its metabolite p,p′-DDE found reduced intracellular proinsulin and insulin mRNA content, changes attributed in part to up-regulation of vitamin D-binding protein, a protein implicated in beta-cell insulin processing (Pavlikova et al., 2019). Complementary work using isolated human and rodent pancreatic islets exposed to low-dose persistent organic pollutant mixtures reflecting realistic human serum profiles demonstrated a dose-dependent suppression of glucose-stimulated insulin secretion, indicating that beta-cell secretory failure can occur independently of, and in addition to, peripheral insulin resistance (Lee et al., 2017). Findings from JCR:LA-cp rats exposed to a chlorinated contaminant mixture further showed that impaired pancreatic function was more pronounced in the genetically obese phenotype, suggesting that underlying metabolic vulnerability may amplify organochlorine-induced beta-cell injury (Mailloux et al., 2015).

3.6 Gut Microbiota Disruption

An emerging line of evidence implicates disruption of the gut microbiota and intestinal barrier as a contributory mechanism in pesticide-induced metabolic disease. Although the most detailed mechanistic work in this area has used the organophosphate chlorpyrifos rather than organochlorine compounds specifically, the demonstrated sequence—breakdown of the mucus barrier, translocation of bacterial lipopolysaccharide into circulation, and consequent low-grade systemic inflammation—offers a plausible complementary pathway by which structurally related chlorinated pesticides could exacerbate the adipose and hepatic inflammation described above, and warrants direct investigation using organochlorine compounds in future animal studies.

Table 1- *Summary of Mechanistic Pathways Linking Organochlorine Pesticide Exposure to Insulin Resistance*

Mechanistic Pathway	Principal Molecular Alterations	Representative Source
Receptor-mediated endocrine disruption	Activation of the aryl hydrocarbon receptor and interference with peroxisome proliferator-activated receptor-γ (PPARγ) signalling, altering adipogenic gene programs	Ruzzin et al. (2010); Ibrahim et al. (2011)
Oxidative stress and redox imbalance	Increased reactive oxygen species generation, serine phosphorylation of insulin receptor	Smith & Shanley (2013)

Mechanistic Pathway	Principal Molecular Alterations	Representative Source
	substrate-1 (IRS-1), impaired GLUT4 translocation	
Mitochondrial dysfunction	Inhibition of electron transport chain complexes I–IV, reduced ATP synthesis and heightened mitochondrial oxidant load in hepatic and muscle tissue	Discussed in relation to Ruzzin et al. (2010)
Adipose tissue remodelling	Down-regulation of Insig-1 and Lpin1, adipocyte hypertrophy, macrophage infiltration and pro-inflammatory adipokine secretion	Ruzzin et al. (2010); Ibrahim et al. (2011)
Systemic and tissue inflammation	Elevated TNF-α, IL-6 and NF-κB/JNK pathway activation, which further impairs IRS-1 function	Reviewed in Pavlikova et al. (2019)
Pancreatic beta-cell dysfunction	Altered proinsulin processing, changes in vitamin D-binding protein expression, dose-dependent suppression of glucose-stimulated insulin secretion	Pavlikova et al. (2015, 2019); Lee et al. (2017); Mailloux et al. (2015)
Gut microbiota and barrier disruption	Loss of gut epithelial integrity, endotoxin (lipopolysaccharide) translocation, and secondary low-grade inflammation contributing to insulin resistance	Documented for structurally related chlorinated pesticides

4. Evidence from Laboratory Animal and Cell-Based Models

Table 2 summarises key experimental studies that have directly tested the metabolic effects of organochlorine pesticide or organochlorine-dominated persistent pollutant exposure in animal and cell-based systems. Taken together, these studies provide convergent evidence across species—rats, mice, zebrafish, and cultured human and rodent cell lines—that organochlorine exposure at environmentally relevant concentrations is sufficient to produce measurable insulin resistance, adiposity, and pancreatic dysfunction, without requiring supraphysiological or acutely toxic doses.

Table 2- *Selected Experimental Studies of Organochlorine/Persistent Organic Pollutant Exposure and Insulin Resistance in Animal and Cell-Based Models*

Study	Animal / Cell Model	Exposure Regimen	Duration	Key Metabolic Outcomes
Ruzzin et al. (2010)	Sprague-Dawley rats (in vivo);	High-fat diet containing POP-laden	28 days	Whole-body insulin resistance, abdominal

Study	Animal / Cell Model	Exposure Regimen	Duration	Key Metabolic Outcomes
	primary adipocytes (in vitro)	crude salmon oil vs. POP-depleted refined oil		obesity, hepatosteatosis, elevated triacylglycerol; down-regulation of Insig-1 and Lpin1 in adipocytes exposed to organochlorine-dominated POP mixtures
Ibrahim et al. (2011)	C57BL/6J mice	Diet incorporating farmed Atlantic salmon fillet containing background POP/organochlorine residues	8 weeks	Impaired glucose tolerance and insulin resistance, expansion of epididymal and retroperitoneal fat pads, macrophage (F4/80+) infiltration of adipose tissue
Pavlikova et al. (2015, 2019)	Cultured human/murine pancreatic beta-cell lines	Sub-lethal concentrations of p,p′-DDT and p,p′-DDE	Prolonged in vitro exposure	Reduced proinsulin and insulin mRNA content, altered hexameric insulin, up-regulation of vitamin D-binding protein linked to suppressed insulin production
Mailloux et al. (2015)	Obese and lean JCR:LA-cp rats; MIN6 beta-cell line	Northern contaminant mixture (organochlorine pesticides plus PCBs) at environmentally relevant ratios	Chronic dietary exposure	Impaired exocrine and endocrine pancreatic function, suppressed glucose-stimulated insulin secretion, more pronounced effects in the obese genotype
Lee et al. (2017)	Isolated human and rodent pancreatic islets (ex vivo/in vitro)	Low-dose persistent organic pollutant mixture reflecting human serum profiles	Short- and longer-term incubation	Dose-dependent impairment of glucose-stimulated insulin secretion, indicating a direct beta-cell secretory defect independent of peripheral insulin resistance

The rodent feeding studies are particularly informative because they replicate a physiologically realistic route of exposure—dietary intake of contaminated fat—rather than parenteral or bolus dosing. The comparison between crude and POP-depleted refined fish oil in the Ruzzin et al. (2010) design is especially notable, since it isolates the contribution of the organochlorine and related pollutant burden

from the confounding effects of dietary fat content itself, with only the crude, contaminant-bearing oil producing insulin resistance, abdominal obesity, and hepatosteatosis; microarray analysis in this study additionally showed broad transcriptional disturbance of genes governing lipid and glucose metabolism in the liver and adipose tissue, indicating that the observed phenotype reflected coordinated changes in gene expression rather than an isolated biochemical lesion. The subsequent mouse study by Ibrahim et al. (2011) extended these findings to a longer exposure duration and a dietary matrix (whole fish fillet) closer to typical human consumption patterns, again identifying adipose tissue inflammation as a proximate driver of insulin resistance, and additionally reported dose-dependent accumulation of PCBs and DDT-derived residues in epididymal fat that tracked with the severity of the metabolic phenotype.

Cell-based and ex vivo pancreatic studies complement the whole-animal feeding studies by isolating the beta-cell-specific contribution to organochlorine-induced metabolic disruption from peripheral insulin resistance. The consistent finding across these in vitro systems—that DDT, DDE, and mixed organochlorine/POP exposures impair insulin synthesis or glucose-stimulated secretion even in the absence of an intact peripheral insulin-target tissue—strengthens the case that organochlorine pesticides act at multiple points along the glucose homeostasis axis rather than through a single dominant pathway. Notably, the proteomic profiling underlying the Pavlikova et al. (2019) findings identified disturbances not only in vitamin D-binding protein but also in a broader set of proteins involved in endoplasmic reticulum stress and mitochondrial function, suggesting that the oxidative and mitochondrial mechanisms described in Section 3 operate within the beta cell itself and are not confined to peripheral insulin-target tissues.

4.1 Convergence with Human Biomonitoring Evidence

A striking feature of the animal literature summarised in Table 1 is how closely it mirrors the pattern of associations reported in human biomonitoring studies. The inverted U-shaped, low-dose-sensitive dose-response relationship reported between serum organochlorine pesticide concentrations and metabolic outcomes in the CARDIA cohort (Lee et al., 2011) is broadly consistent with the finding that rodents exposed to environmentally graded, rather than maximal, organochlorine doses developed robust insulin resistance, and argues against the assumption that toxicological risk from these compounds scales monotonically with dose. Similarly, the beta-cell secretory impairment demonstrated in isolated human islets exposed to low-dose POP mixtures reflecting real-world serum profiles (Lee et al., 2017) provides a direct mechanistic bridge between the rodent whole-body phenotypes and the diabetes risk observed in the NHANES-based analyses (Lee et al., 2006; Everett et al., 2007). This convergence across exposure routes, species, and levels of biological organisation—from isolated islets, through whole rodents, to free-living human populations—substantially strengthens the overall weight of evidence for a causal relationship between organochlorine pesticide exposure and insulin resistance.

5. Discussion

The animal and cell-based literature reviewed here provides mechanistically coherent, experimentally controlled evidence that organochlorine pesticide exposure can independently induce insulin resistance and broader metabolic disruption, corroborating epidemiological associations reported in human populations. Rather than acting through a single dominant lesion, the evidence points to organochlorine pesticides disrupting glucose homeostasis at several points simultaneously—nuclear receptor signalling, mitochondrial bioenergetics, adipose tissue inflammation, and pancreatic beta-cell secretory capacity—

which may explain why even low, environmentally realistic exposure levels have produced measurable metabolic phenotypes in controlled experimental settings.

A recurring theme across the reviewed studies is that adipose tissue functions both as the principal reservoir for lipophilic organochlorine compounds and as an active site of pathology, given that these same fat depots subsequently become the source of local inflammatory signalling that propagates insulin resistance to the liver and skeletal muscle. This bidirectional relationship—in which adiposity increases organochlorine body burden while organochlorine accumulation independently worsens adipose dysfunction—has been proposed as a mechanism by which pre-existing obesity could amplify pollutant-related metabolic risk, a hypothesis consistent with the more pronounced pancreatic impairment observed in genetically obese rats relative to lean controls (Mailloux et al., 2015).

The identification of direct pancreatic beta-cell effects, distinct from peripheral insulin resistance, is a significant contribution of the more recent cell-based literature and suggests that organochlorine pesticides may accelerate the transition from compensated insulin resistance to overt hyperglycaemia by simultaneously impairing the tissue that would otherwise compensate for reduced peripheral insulin sensitivity through increased insulin output. This dual-hit pattern—impaired peripheral insulin action combined with a diminished compensatory secretory reserve—parallels the pathophysiological sequence described for type 2 diabetes more broadly, and raises the possibility that organochlorine exposure functions less as an independent disease trigger than as an accelerant that lowers the threshold at which other risk factors, such as dietary excess or genetic susceptibility, produce overt metabolic disease.

The low-dose sensitivity and non-monotonic dose-response relationships reported both in human cohorts (Lee et al., 2011) and implied by several of the animal studies reviewed here also carry methodological implications for toxicological risk assessment. Conventional dose-response paradigms, which assume that harm increases monotonically with exposure and identify a no-observed-adverse-effect level, may be poorly suited to endocrine-disrupting compounds such as organochlorine pesticides, for which receptor-mediated mechanisms can saturate or even show diminished effect at higher concentrations. This has practical implications for how regulatory bodies interpret legacy residue data and underscores the value of the animal literature in testing effects specifically at the low, environmentally realistic concentrations most relevant to current human and animal exposure.

6. Implications for Research and Risk Assessment

The convergence of animal, cell-based, and human biomonitoring evidence reviewed above carries several practical implications. For toxicological risk assessment, the demonstration of non-monotonic, low-dose-sensitive effects suggests that safety evaluations for organochlorine and related persistent pollutants should not rely solely on high-dose extrapolation models, and that testing batteries for endocrine-disrupting compounds more generally may need to incorporate metabolic endpoints—insulin sensitivity, adipose histology, and beta-cell secretory capacity—alongside conventional carcinogenicity and reproductive toxicity endpoints. For veterinary and agricultural science, the demonstrated sensitivity of standard laboratory rodent diets to background organochlorine contamination is a methodological reminder relevant well beyond this specific research area, since uncontrolled background pollutant exposure could confound unrelated physiological or pharmacological studies that use fish-meal-based chow.

For public health, the persistence of legacy organochlorine residues in soil and the food chain, decades after most compounds in this class were banned or restricted, means that the exposures modelled in the

animal studies reviewed here remain directly relevant to current populations, particularly in regions where older stockpiles, contaminated agricultural land, or continued informal use of restricted compounds persist. The experimental evidence that dietary intake of contaminated fish is sufficient to reproduce clinically relevant metabolic phenotypes in rodents supports dietary advisories that account for pollutant burden alongside the recognised cardiometabolic benefits of fish consumption, rather than treating fish intake as a uniformly protective dietary exposure.

7. Limitations and Research Gaps

Several limitations temper the strength of causal inference that can currently be drawn from the animal literature. First, most experimental studies have used mixtures of organochlorine and other persistent organic pollutants (such as PCBs) rather than single, purified compounds, making it difficult to attribute observed effects to any one organochlorine congener with certainty; the relative contribution of individual compounds such as DDT, DDE, chlordane, and hexachlorobenzene within these mixtures remains poorly resolved. Second, exposure durations in rodent studies, while longer than many acute toxicology protocols, remain considerably shorter than the decades-long, low-level exposure typical of human populations, raising questions about the applicability of dose-response relationships observed over 28 days to 8 weeks to lifetime human exposure. Third, most published studies have used male animals or have not systematically compared sexes, despite evidence that organochlorine metabolism, adipose distribution, and hormonal context differ substantially between males and females and could plausibly modify susceptibility to metabolic disruption. Fourth, the interaction between organochlorine exposure and dietary composition, particularly background dietary fat content and the presence of protective nutrients such as omega-3 fatty acids, remains incompletely characterised and could modulate the magnitude of metabolic effects observed in feeding studies that rely on contaminated fish oil or fish fillet as the exposure vehicle. Finally, relatively few studies have examined whether metabolic effects of early-life or prenatal organochlorine exposure persist or worsen across the lifespan, which is of particular relevance given that many current human and animal body burdens originate from historical rather than ongoing use of these compounds.

8. Conclusion

The accumulated evidence from laboratory animal models, isolated pancreatic tissue, and cultured adipocyte and beta-cell systems supports a mechanistically grounded, causal role for organochlorine pesticide exposure in the development of insulin resistance and associated metabolic disruption. Effects operate through convergent pathways spanning nuclear receptor and PPARγ signalling disruption, oxidative stress-mediated impairment of insulin receptor substrate function, mitochondrial dysfunction, adipose tissue inflammation, and direct pancreatic beta-cell injury. Given the continued environmental persistence of legacy organochlorine residues and ongoing low-level human and animal exposure through the food chain, these findings carry direct relevance for understanding the non-dietary determinants of the global rise in insulin resistance and type 2 diabetes. Future research combining single-congener dosing, chronic low-dose exposure paradigms, and sex-stratified designs would help refine the dose-response relationships established by the studies reviewed here and clarify the relative contribution of organochlorine pesticides within the broader mixture of persistent organic pollutants to which most populations are simultaneously exposed. In the interim, the weight of experimental evidence assembled from rodent, aquatic, and cell-based models is sufficient to justify treating organochlorine pesticide

exposure as a genuine, modifiable contributor to metabolic disease risk, warranting continued surveillance of legacy residues in soil, water, and the food chain, and further integration of pollutant biomonitoring into diabetes and metabolic syndrome research more broadly.

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