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Consensus statement

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Consensus on the key characteristics of metabolism disruptors

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Abstract

Metabolism-disrupting agents (MDAs) are chemical, infectious or physical agents that increase the risk of metabolic disorders. Examples include pharmaceuticals, such as antidepressants, and environmental agents, such as bisphenol A. Various types of studies can provide evidence to identify MDAs, yet a systematic method is needed to integrate these data to help to identify such hazards. Inspired by work to improve hazard identification of carcinogens using key characteristics (KCs), we developed 12 KCs of MDAs based on our knowledge of processes underlying metabolic diseases and the effects of their causal agents: (1) alters function of the endocrine pancreas; (2) impairs function of adipose tissue; (3) alters nervous system control of metabolic function; (4) promotes insulin resistance; (5) disrupts metabolic signalling pathways; (6) alters development and fate of metabolic cell types; (7) alters energy homeostasis; (8) causes inappropriate nutrient handling and partitioning; (9) promotes chronic inflammation and immune dysregulation in metabolic tissues; (10) disrupts gastrointestinal tract function; (11) induces cellular stress pathways; and (12) disrupts circadian rhythms. In this Consensus Statement, we present the logic that revealed the KCs of MDAs and highlight evidence that supports the identification of KCs. We use chemical, infectious and physical agents as examples to illustrate how the KCs can be used to organize and use mechanistic data to help to identify MDAs.

Sections

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Introduction

The idea that chemical, physical and infectious agents have properties, called key characteristics (KCs), that confer a potential hazard was first developed for carcinogens[1] at the International Agency for Research on Cancer (IARC) and was based on the known properties of established human carcinogens identified by that agency. This idea led to the KC framework for systematically analysing the mechanistic literature as part of a weight-of-the-evidence approach to carcinogenic hazard identification evaluating epidemiological, animal bioassay and mechanistic data streams[2,3]. The KCs of human carcinogens are now widely used[4–6] and have been endorsed by the National Academies of the USA[7]. A National Academies report also suggested that KCs of other types of toxicants should be developed[7]. The KCs of endocrine-disrupting chemicals[8], reproductive toxicants[9,10], hepatotoxicants[11], cardiovascular toxicants[12] and immunotoxic agents[13] have been published. Given the widespread interest in the KC framework, especially its application in identifying endocrine disruptors, we have expanded the KC concept to metabolism disruptors. Together with a combination of complementary information, these new KCs can be used to provide a framework to identify and characterize chemical, infectious and physical agents that might have unintended effects on human metabolism, potentially leading to obesity, diabetes mellitus, metabolic dysfunction-associated steatotic liver disease (MASLD; also known as non-alcoholic fatty liver disease) and the metabolic syndrome. Metabolism-disrupting agents (MDAs) might have an often under-appreciated role in the global epidemics of these diseases[14–16].

Metabolism refers to all life-sustaining biochemical reactions occurring in living organisms, which can be divided into three categories. First, conversion of nutrient fuels into energy (catabolism). Second, generation of macromolecules from small molecular 'building-block' components, which are usually derived from nutrients (anabolism). Third, neutralization and elimination of metabolic waste (excretion). The regulation of metabolism is an intricate process coordinated by hormones from various tissues, including the classic endocrine organs (such as the thyroid), as well as adipose tissue, liver, the gastrointestinal tract and muscle. The actions of these hormones are integrated and coordinated by the central nervous system, in which specialized neurons control and integrate peripheral hormonal and nutrient signals (homeostatic pathway) and control of the reward and addiction pathways (hedonic pathway)[17,18].

Some of the best examples of chemical agents that disrupt metabolism and produce weight gain are pharmaceuticals, such as antidepressants (for example, amitriptyline, trazodone, sertraline and escitalopram) and some antidiabetic drugs (for example, thiazolidinediones and sulfonylureas)[19–22]. Generally, excess weight gain is considered minor relative to the beneficial effects of these drugs for patients. However, well-established knowledge of how these pharmaceuticals disrupt metabolism can inform development of a set of KCs for MDAs. Environmental chemicals, such as dichlorodiphenyltrichloroethane (DDT), tributyltin (TBT) and bisphenol A (BPA), are also known to disrupt metabolism, and the probable mechanisms underlying these effects are becoming better understood[14] (Box 1). Chemical food additives are another chemical class that disrupts metabolism. For example, *trans*-fatty acids promote MASLD and metabolic dysfunction-associated steatohepatitis (MASH; also known as non-alcoholic steatohepatitis) in humans[23], and some additives and emulsifiers used in ultraprocessed foods are also MDAs in animals and humans[14]. It is important to note that, unlike our exposure to pharmaceuticals, our exposure to environmental chemicals and food additives is mostly involuntary.

MDAs also include a variety of infectious and physical agents. Infectious examples include human immunodeficiency virus (HIV)[24] and adenovirus 36 (ref. 25). Physical agents that disturb sleep and/or disrupt circadian rhythms, such as night work, blue light exposure and noise (such as urban versus rural noise environments), are also increasingly associated with metabolic disruption[26,27]. The mechanisms by which circadian disruption and physical agents disrupt metabolism are less defined than those for pharmaceutical and infectious agents, as are the mechanisms by which environmental chemical agents disrupt normal metabolism.

In this Consensus Statement, we use available mechanistic knowledge on pharmaceutical, chemical, physical and biological agents to identify the KCs of metabolism disruptors. We provide examples demonstrating the use of these KCs to characterize the toxicity of various agents, recognizing that some substances might initiate cascades of events and exhibit multiple KCs. We provide recommendations for assessing how previously untested chemicals might affect specific KCs and conclude that understanding how substances cause metabolic disruption will facilitate the development of improved tests to identify MDAs. This approach will enable a more comprehensive mechanistic understanding of how environmental chemicals and other agents disrupt metabolism and cause adverse outcomes, such as obesity, diabetes mellitus (both type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM)), MASLD and MASH.

Methods

We assembled an international group of experts with knowledge of metabolic diseases, chemical and pharmaceutical hazard assessment and MDAs. Initial experts were chosen by M.A.L.M. and B.B. from attendees at a HEEDS Workshop (organized by a panel led by J.J.H.) held at the Wingspread Conference Center, Racine, WI, USA, on 7 September 2022. J.J.H., M.A.L.M. and B.B. have written extensively about MDAs. Participants M.C.C., D.C., S.K. and R.M.S. were chosen for their medical qualifications, clinical experience and expertise in the field of metabolism disruption. A.N. was chosen for his expertise in metabolic disruption, especially in relation to BPA exposure, and to bring a European perspective. E.A. was chosen for her expertise in metabolism disruption and as an employee of Health Canada. L.Z. was selected because she was head of the main risk assessment organization in the California Environmental Protection Agency throughout the process of KC development, and has extensive experience with the KCs in the regulatory environment. K.Z.G. was selected for her extensive experience in applying the KCs at the International Agency for Research on Cancer and now at the National Academies. C.J.R. was added to the group after the Wingspread meeting to bring the perspective of the pharmaceutical industry and because of his extensive knowledge of metabolism-disrupting drugs. M.T.S. and C.M.M. have extensive experience in coordinating projects on the KCs and bringing them to fruition. All decisions made by the group were built from consensus with everyone in agreement after a full and robust discussion.

A list of KCs of MDAs was originally developed at the 2-day in-person workshop at Wingspread and discussed extensively at biweekly teleconferences. Three working groups proposed KCs based on their expertise and these were discussed extensively at the workshop, aiming to maximize inclusivity of mechanistic pathways, while minimizing the number of KCs. This process led to the identification of 12 KCs (Fig. 1 and Box 2) which were agreed upon based on an evaluation of the scientific literature on obesity, diabetes mellitus, MASLD and the metabolic syndrome. Furthermore, the role and mechanisms

by which these conditions are produced by well-established causes, such as pharmaceuticals and certain environmental agents, was also taken into account. These KCs are described with non-exhaustive but relevant exemplary agents and mechanisms. We recognize that some of the KCs we describe might have beneficial effects on certain tissues in the organism while contributing to adverse outcomes in others. We next selected six chemicals to illustrate how different MDAs might have one or more of the KCs leading to the hazard of metabolism disruption. The pharmaceuticals glucocorticoids, atypical antipsychotics (AAPs) and streptozotocin (Supplementary Table 1) and the environmental chemicals BPA, DDT and TBT (Box 1; Supplementary Table 2) were selected by the working group to describe some of the evidence for each KC in Supplementary Tables 1 and 2. The group considered these examples as providing the best summary of the diverse mechanisms by which metabolic disruption can occur.

The KCs of MDAs

We identified 12 KCs, as described in this section. Figure 1 and Box 2 list each KC and provide a summary of the mechanisms involved, and Supplementary Tables 1 and 2 provide detailed examples of pharmaceutical and environmental agents that possess these KCs.

KC1: alters function of the endocrine pancreas

Loss of sufficient β-cell function and number underlies the pathogenesis of diabetes mellitus. The inability of pancreatic islet β-cells to produce sufficient insulin to meet metabolic demands results in hyperglycaemia and clinical diabetes mellitus[28] (Fig. 1). The classic example of an MDA that produces this effect is the drug streptozotocin, which destroys β-cells (Supplementary Table 1). Loss of β-cells can be the result of their immune-mediated destruction, which is the pathophysiological basis of type 1 diabetes mellitus. Intriguingly, some MDAs might augment this process, including BPA[29,30]. In addition to cellular loss, hyperglycaemia can result from functional defects in β-cells that manifest as a dampening of glucose-induced insulin secretion, which might arise from long-term exposure to free fatty acids as observed in vitro and in vivo in animal models[31,32]. Importantly, it is the loss of β-cell function over time that is most closely linked to glycaemic deterioration despite treatment in T2DM[33,34].

Environmental chemicals that decrease glucose-induced insulin secretion and/or biosynthesis of proinsulin and insulin in experimental animals include dioxins[35], perfluorooctanoic acid (PFOA)[36], bisphenol S[37], di(2-ethylhexyl) phthalate (DEHP)[37] and inorganic arsenic[38–40]. Indeed, dioxin suppresses the influx of calcium in glucose-stimulated β-cells, which is known to attenuate glucose-induced insulin secretion[41]. Insulin hypersecretion can generate primary hyperinsulinaemia that promotes obesity and insulin resistance, ultimately reducing functional β-cell mass[42,43]. For example, sulfonylureas are older drugs used clinically to promote insulin secretion, but, unlike glucose, they do not complementarily increase biosynthesis of proinsulin and insulin. As such, compared with other glucose-lowering medications, sulfonylureas exhibit worse long-term duration of activity, probably resulting from progressive depletion of the insulin secretory storage pool, reduced insulin secretory capacity and eventually worsening T2DM[44–46]. Ultimately, long-term treatment with sulfonylureas is associated with accelerated β-cell failure[47] and the clinical need for exogenous insulin administration[48].

Pancreatic α-cells release glucagon when blood levels of glucose are low (Fig. 1). Although α-cells are not their sole pharmacological target, commonly used antidiabetic drugs reduce glucose-dependent glucagon secretion, which is abnormally increased in T2DM; these drugs include the amylin analogue pramlintide and agents that modify the incretin system. Information about environmental agents that affect glucagon secretion is scarce. However, PFOA[49], BPA, bisphenol S, cadmium and DEHP[50] all decreased glucagon secretion induced by low glucose levels in αTC1-9 cells.

KC2: impairs function of adipose tissue

Adipocytes are critical players in maintaining metabolic health, mainly owing to their substantial capacity to take up and store triglycerides and to take up and use glucose in response to insulin (Fig. 1). Adipocytes also produce hormones that coordinate metabolic functions, and disruption of these functions contributes to obesity. Some examples are visceral adipose tissue hypertrophy, adipose tissue inflammation, insulin resistance and T2DM. Selective peroxisome proliferator-activated receptor-γ (PPARγ) full-activators, such as rosiglitazone and pioglitazone (which are insulin-sensitizing pharmaceutical thiazolidinediones), promote the development of healthy white adipocytes through adipogenesis[51–54]. These adipocytes readily take up glucose, are insulin-sensitive and

Box 1 | Sources of exposure to metabolism disruptors

Bisphenol A is oestrogenic and also acts as an androgen and thyroid hormone receptor antagonist. It is widely used to make polycarbonate plastics, epoxy resins, food contact materials and thermal papers. It is one of the highest production volume chemicals and is detected in almost everyone[272].

Phthalates are esters of phthalic acid used to promote flexibility, transparency and durability in plastic products. They are also found in food packaging and many household and personal care products, including children's toys, air fresheners and medical equipment[273].

Tributyltin is a fungicide used on high-value crops and as an antifouling paint for boats that contaminates seafood, and is a contaminant in polyvinyl chloride (PVC) plastics. It is highly lipid soluble and remains a global contaminant[274].

Polybrominated diphenyl ethers (PBDEs) are a family of 209 persistent halogenated congeners containing bromine, and are used as flame retardants in consumer products, including furniture. They were removed from the market[275] but continue to be found in humans, especially in adipose tissue[276]. Their replacements were organophosphate flame retardants, which, similar to PBDEs, are persistent and can leach out of treated materials, including PVC plastics.

Perfluoroalkyl and polyfluoroalkyl substances are a persistent and bioaccumulative class of many thousands of chemicals that are used to confer waterproof, greaseproof and non-stick properties to consumer products. They are also used in fire-fighting foams[277].

Dichlorodiphenyltrichloroethane (DDT) is a persistent, bioaccumulative pesticide used to prevent diseases (such as malaria and typhus) carried by mosquito vectors. DDT is banned in many countries but is still used in others (such as Kenya and South Africa). It is still found in many people worldwide. Dichlorodiphenyldichloroethylene is a persistent metabolite of DDT that is also a persistent organic pollutant and common contaminant of the food supply, and is found in almost everyone worldwide[244,278].

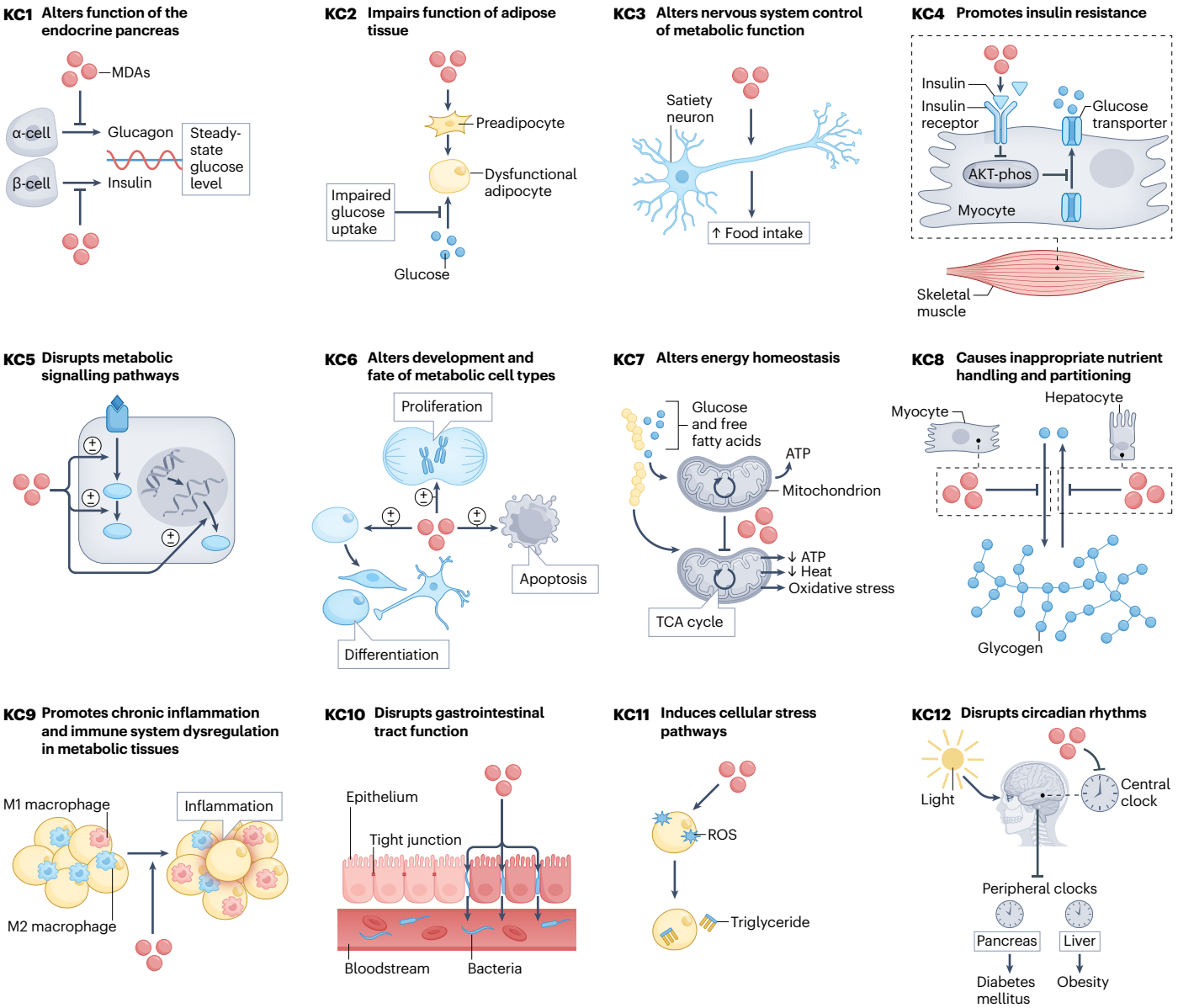

Fig. 1 | The key characteristics of metabolism-disrupting agents illustrated with specific mechanistic examples. Red circles are metabolism-disrupting agents (MDAs). The plus or minus symbol indicates that an MDA can increase or decrease processes and effects; the blocked lines indicate that an MDA can interfere with or block an effect, and the arrows indicate that an MDA can influence a process. KC1: an MDA can alter the function of the endocrine pancreas by, for example, interfering with glucagon and insulin secretion by pancreatic α-cells and β-cells, respectively, leading to disruption of steady-state glucose control. KC2: an MDA can impair the function of adipose tissue by, for example, impairing differentiation, resulting in an altered balance between white, beige and brown adipocytes and the development of a dysfunctional adipocyte with impaired glucose uptake. KC3: an MDA can alter nervous system control of metabolic function by, for example, acting on food intake and satiety neurons to stimulate food intake. KC4: an MDA can promote insulin resistance. KC5: an MDA can disrupt metabolic signalling pathways. KC6: an MDA can alter the development and fate of metabolic cell types by, for example, affecting proliferation, differentiation and apoptosis. KC7: an MDA can alter energy homeostasis by, for example, impairing thyroid hormone synthesis. KC8: an MDA can cause inappropriate nutrient handling and partitioning by, for example, impairing glucose storage as glycogen in the liver. KC9: an MDA can promote chronic inflammation and immune dysregulation in metabolic tissues by, for example, promoting metabolic inflammation in adipose tissue that increases the number of inflammatory M1 macrophages. KC10: an MDA can disrupt gastrointestinal tract function by, for example, disrupting and/or opening the tight junctions in the intestinal barrier. KC11: an MDA can induce cellular stress pathways by, for example, increasing the levels of reactive oxygen species (ROS) in adipocytes resulting in a net increase in triglyceride stores. KC12: an MDA can disrupt circadian rhythms by impairing the hypothalamic suprachiasmatic nucleus or nuclei clock leading to downstream effects on peripheral clocks and the induction of obesity and diabetes mellitus. AKT-phos, AKT phosphorylation; TCA, tricarboxylic acid cycle.

Box 2 | Examples of some effects or mechanisms associated with key characteristics 1–12

Additional details, along with examples of agents that cause them, are provided in the descriptions of each key characteristic (KC) and in Supplementary Tables 1 and 2. We note that some of the KCs overlap partially. For example, in KC3, the glucagon-like peptide 1 (GLP1) pathway overlaps with KC10; activation of peroxisome proliferator-activated receptor-γ (PPARγ) in KC5 overlaps with KC6; destruction of β-cells in KC6 overlaps with KC1; KC8 overlaps with a part of KC3.

KC1: alters function of the endocrine pancreas

- Destroys pancreatic islet β-cells leading to hyperglycaemia and clinical diabetes mellitus.
- Reduces β-cell function and number, impairing insulin release and glucose homeostasis.
- Dampens glucose-induced insulin secretion.
- Induces insulin hypersecretion leading to primary hyperinsulinaemia.
- Disrupts α-cell functional mass, impairing glucagon release and glucose homeostasis.

KC2: impairs function of adipose tissue

- Disrupts adipocyte capacity to take up and store triglycerides, to take up and utilize glucose in response to insulin, and to produce hormones that coordinate metabolic functions.
- Stimulates the differentiation of preadipocytes into adipocytes and influences the balance between white, beige and brown adipocytes.
- Promotes the development of dysfunctional adipocytes, with impaired glucose uptake and insulin-responsive signalling.

KC3: alters nervous system control of metabolic function

- Alters responsiveness to leptin, insulin, ghrelin, GLP1 and macronutrients, and potentially factors derived from the gut microbiome.
- Disrupts hypothalamic responsiveness to physiological signals.
- Constitutively engages hedonic circuits to disrupt the normal brakes on food intake.
- Modulates hormonal, neurotransmitter or nutrient-dependent signalling by hypothalamic neurons or neurons in other linked nuclei within the brain, thus impairing energy homeostasis.
- Acts on the food intake and satiety neurons to stimulate food intake.
- Causes reduced physical activity or basal metabolic rate through the peripheral nervous system, promoting positive energy balance.

KC4: promotes insulin resistance

- Reduces response to insulin in insulin-responsive tissues, such as liver, muscle, brain and adipose tissues at the transcriptional and functional levels; the ensuing increased blood levels of insulin to compensate for the resistance can cause weight gain.
- Induces chronic hyperinsulinaemia, resulting from endogenous pancreatic β-cells, leading to insulin-induced insulin resistance that exacerbates type 2 diabetes mellitus pathogenesis.
- Causes skeletal muscle insulin resistance resulting in reduced glucose uptake, reduction in AKT phosphorylation, reduction in GLUT4 (glucose transporter responsible for insulin-related glucose transport into cells) and intramuscular lipid accumulation.
- Causes insulin resistance in adipocytes leading to decreased GLUT4 expression, reduced glucose uptake and increased lipolysis.

KC5: disrupts metabolic signalling pathways

- Binds to PPARγ–retinoid acid receptor (RXR), creating downstream effects that predispose multipotent mesenchymal stromal stem cells (MSCs) to favour the adipogenic pathway and differentiate into adipocytes.
- Acts via oestrogen, androgen or thyroid receptors or the glucocorticoid receptor.
- Disrupts receptor-based signalling pathways (for example, the insulin and leptin receptors) leading to signal toxicity (for example, disruption of epidermal growth factor (EGF) receptor phosphoprotein signalling with effects on the phosphoinositide 3-kinase signalling pathway and other metabolic signalling pathways). Decreases EGF-mediated EGF receptor internalization and signalling, affecting hepatic lipid and carbohydrate metabolism, inflammation, fibrosis and non-alcoholic steatohepatitis.
- Epigenetically alters chromatin structure and inhibits the expression of insulin-degrading enzyme.

KC6: alters development and fate of metabolic cell types

- Alters the commitment of pluripotent stem cells, leading to changes in the number and type of various metabolic cells.
- Promotes adipogenic differentiation of MSCs or preadipocytes via PPARγ or RXR activation.
- Induces adipogenic differentiation of MSCs but produces dysfunctional adipocytes with various deficiencies.
- Destroys pancreatic β-cells, resulting in insulinopenic diabetes mellitus.
- Decreases β-cell mass by enhancing apoptosis.
- Reduces the volume of numerous regions of the developing brain; for example, decreased prefrontal cortex volumes resulting from impairment of neuronal progenitor cell proliferation.
- Disrupts neurogenesis by affecting neuronal stem cell proliferation and viability, influencing stem cell fate and enhancing differentiation of neuronal progenitors into neurons with in utero exposure manifesting as disrupted neurogenesis in some areas of the embryonic mouse brain.

KC7: alters energy homeostasis

- Alters cellular bioenergetics, such as mitochondrial dysfunction (for example, mitochondrial uncoupling) or perturbs neuroendocrine pathways that regulate peripheral tissues contributing to physical activity and energy expenditure.
- Reduces physical activity and thermogenesis.
- Decrease body heat without decreasing physical activity.
- Alters metabolic set points, favouring energy storage.
- Decreases food efficiency, favouring energy storage.
- Antagonizes β-adrenergic receptors, reducing resting energy expenditure in humans.
- Disrupts thyroid hormone action by impairing thyroid hormone synthesis.

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KC8: causes inappropriate nutrient handling and partitioning

- Alters the synthesis, release, transport, storage and breakdown of nutrients, such as carbohydrates, lipids and amino acids.
- Reduces glucose stored as glycogen in the liver and in muscle.
- Impairs glucose mobilization from glycogen to prevent hypoglycaemia.
- Induces sarcopenia, leading to altered postprandial glucose uptake and storage.
- Adversely alters muscle health.

KC9. Promotes chronic inflammation and immune dysregulation in metabolic tissues

- Induces metabolic inflammation, which is chronic inflammation associated with increasing visceral adiposity and the development of insulin resistance.
- Induces pro-inflammatory cytokines and lipids (for example, TNF, IL-6, IL-1b, IFN and PAI1) in tissues of individuals affected by metabolically unhealthy obesity.
- Causes sequestration of substantial amounts of lipids present in tissues affected by obesity by macrophages known as foam cells, which fuel the metabolic consequences of unhealthy obesity and unhealthy ageing in general.
- Activates macrophages and other innate immune cell types, which are enriched in unhealthy weight gain by lipids, including ceramides, phospholipids and saturated long-chain fatty acids.
- Disrupts innate immunity and promotes inflammation.

KC10: pisrupts gastrointestinal tract function

- Impairs nutrient and water absorption.
- Modifies microbial populations (Box 3).
- Impairs the normal intestinal barrier of microbiome-derived mediators through decreased intestinal mucus production, epithelial tight junction proteins and antimicrobial peptide production.
- Disrupts gut-derived hormones that regulate systemic metabolism, such as the hunger hormone ghrelin.
- Regulates other gut hormones implicated in systemic metabolism, such as, GLP1.

KC11: induces cellular stress pathways

- Induces oxidative stress resulting from mitochondrial dysfunction (see KC7).
- Produces endoplasmic reticulum stress, resulting in increased reactive oxygen species production from mitochondria in adipocytes, liver cells or pancreatic β-cells (see KC1 and KC6).
- Cellular stress or disruption of ameliorating pathways alters cellular homeostasis and might change cell fate (see KC6).

KC12: disrupts circadian rhythms

- Alters circadian biology and/or sleep.
- Disrupts circadian biology and promotes metabolic dysfunction.
- Disrupts aspects of circadian rhythms or clock biology.

express anti-inflammatory adipokines such as adiponectin, apelin and fibroblast growth factor 21 (refs. 53,55). Healthy white adipocytes can also undergo conversion to thermogenic beige or brite adipocytes in response to bodily cold exposure or treatment with thyroid hormone or β_3-adrenergic receptor agonists[56] (Fig. 1). This increased adipogenesis by selective PPARγ full-activating drugs provides an appropriate place to store adipose tissue safely and thus improve global insulin sensitivity in T2DM, obesity and the metabolic syndrome, but it does come with body weight gain[57]. Some MDAs can promote the development of dysfunctional adipocytes, which have impaired glucose uptake and insulin-responsive signalling[58]. These MDAs include glucocorticoid receptor agonists, tolylfluanid (a fungicide), the PPARγ and retinoid acid receptor (RXR) activator TBT and chemicals that selectively activate the 9-*cis*-RXR.

KC3: alters nervous system control of metabolic function

The hypothalamus regulates hunger, satiety, food-seeking behaviour, energy expenditure and glycaemic control via homeostatic and hedonic pathways[59]. Impaired hypothalamic control of metabolic homeostasis is a driver of obesity; such impairments include those reflecting altered responsiveness to hormones (for example, leptin, insulin, ghrelin and glucagon-like peptide 1 (GLP1)), macronutrients and potentially factors derived from the gut microbiome[18,60]. Excess consumption of specific nutrients, including fats and particularly sugar, disrupts hypothalamic responsiveness to physiological signals and can also constitutively engage hedonic circuits to disrupt the normal brakes on food intake[18,60]. Environmental exposures that modulate hormonal, neurotransmitter or nutrient-dependent signalling by hypothalamic neurons or neurons in other linked nuclei within the brain can similarly impair energy homeostasis[14] (Fig. 1). MDAs, including BPA, phthalates, TBT and organophosphate flame retardants, act on food intake and satiety neurons to stimulate food intake in rodent models[14]. Chemical exposures that tend to reduce physical activity, such as prenatal exposure to lead or BPA[61], or those that can reduce basal metabolic rate through the peripheral nervous system, such as DDT in animal models[62] and perfluorooctane sulfonic acid in humans[63], can also promote positive energy balance via the nervous system, and can thus act as MDAs. AAP medications (discussed in the section 'AAP medications') have a strong effect on appetite control and energy metabolism[64–67].

KC4: promotes insulin resistance

Insulin resistance is defined as the reduced response to insulin in insulin-responsive tissues such as the liver, muscle, brain and adipose tissues. Diminished responses to insulin in these tissues results in blunted responses at the transcriptional and functional levels, along with increased blood levels of insulin to compensate for the resistance, which can cause weight gain (Fig. 1). Chronic hyperinsulinaemia, resulting from insulin secretion from endogenous pancreatic β-cells, via pharmacological treatment with sulfonylureas or exogenous insulin, can eventually lead to insulin-induced insulin resistance that exacerbates T2DM pathogenesis. Fructose and non-nutritive sweeteners also cause hepatic insulin resistance in humans[68], as does PFOA, which has been associated with insulin resistance in epidemiological studies[69]. In skeletal muscle, insulin resistance results in reduced glucose uptake, reductions in AKT phosphorylation, reduced glucose transporter 4 levels and disrupted intracellular trafficking (this glucose transporter

is responsible for insulin-related glucose transport into cells) and intramuscular lipid accumulation. BPA exposure reduced AKT phosphorylation and glucose transporter 4 translocation in the muscle of exposed rats[70,71]. Insulin resistance in adipocytes is associated with decreased expression of the gene encoding glucose transporter 4, reduced glucose uptake and increased lipolysis. Several environmental MDAs alter these events in vitro and in rodents[14].

KC5: disrupts metabolic signalling pathways

Metabolism is in part controlled by hormones and growth factors that act via specific receptor-mediated pathways (Fig. 1). The so-called master regulator of adipogenesis[72], PPARγ, is a ligand-activated transcription factor that acts as a heterodimer with RXR to regulate white adipose tissue development[72]. Some obesogenic MDAs, such as TBT, bind to the PPARγ–RXR heterodimer, creating downstream effects that predispose multipotent mesenchymal stromal stem cells (MSCs) to favour the adipogenic pathway and differentiation into adipocytes[53,73]. Other nuclear receptors and transcription factors also have important roles in metabolic signalling that lead to weight gain[53] and metabolic dysfunction; and these pathways can be disrupted by MDAs[74–76]. BPA can disrupt metabolism via the oestrogen, androgen or thyroid hormone receptor pathways[77], whereas the fungicide tolylfluanid has a more restricted action as it only acts on the glucocorticoid receptor[78]. Metabolism is not exclusively controlled by nuclear receptors and transcription factors. Cell surface receptor-based signalling pathways (such as the insulin and leptin receptors) also regulate metabolism, and can be disrupted by MDAs. An emerging example is disruption of epidermal growth factor receptor (EGFR) signalling by environmental exposures, including polychlorinated biphenyls (PCBs), bisphenols, flame retardants and pesticides[79,80]. Similar to the insulin signalling cascade, EGFR signal transduction affects the phosphoinositide 3-kinase signalling pathway and other metabolic signalling pathways. PCBs decrease EGF-mediated EGFR internalization and signalling, which affects hepatic lipid and carbohydrate metabolism, inflammation, and the development of fibrosis and MASH[79]. MDAs can also influence metabolic signalling pathways epigenetically[81]. For example, exposing pregnant F0 mice to TBT leads to obesity in male descendants up to the F4 generation without further exposure in the descendants[82] by epigenetically altering chromatin structure and inhibiting the expression of insulin-degrading enzyme[83] (note that ref. 83 is a preprint).

KC6: alters development and fate of metabolic cell types

MDAs alter the commitment of pluripotent stem cells, leading to changes in the number and type of various metabolic cells, particularly adipocytes, pancreatic β-cells and neurons[84] (Fig. 1). Pharmaceutical thiazolidinediones and the agricultural chemicals quinoxyfen and spirodiclofen also promote adipogenic differentiation of mouse MSCs or preadipocytes via PPARγ activation, whereas the fungicide fludioxonil does so via activation of RXR in mice[58,84]. Thiazolidinediones also induce a MASLD phenotype in mice[85] and affect the heart in humans[86]. In rodents, MDAs such as BPA, phthalates, polybrominated diphenyl ethers (PBDEs), DDT, parabens, TBT and non-nutritive sweeteners[87] can stimulate the differentiation of preadipocytes into adipocytes and can influence the balance between white, beige and brown adipocytes[14]. Experimental agents, such as alloxan, streptozotocin and the rodenticide pyrinuron, destroy pancreatic β-cells, resulting in insulinopenic diabetes mellitus[15]. Furthermore, nicotine exposure across the fetal and neonatal period also results in decreased β-cell mass due to enhanced apoptosis with resultant impaired glycaemic control in rats[88]. Nicotine also reduces the volume of multiple regions of the developing human brain, with effects differing based upon the timing of exposure[89]. A decreased volume of the prefrontal cortex results from nicotine-mediated impairment of neuronal progenitor cell proliferation in mice[90]. Similarly, BPA disrupts neurogenesis by affecting neuronal stem cell proliferation and viability, which influences stem cell fate and enhances differentiation of neuronal progenitors into neurons; in utero exposure manifests as disrupted neurogenesis in some areas of the embryonic mouse brain[91].

KC7: alters energy homeostasis

Imbalances in energy storage and expenditure induce metabolic dysfunction. Energy homeostasis can be disrupted by alterations in cellular bioenergetics, such as mitochondrial dysfunction, and by perturbations in neuroendocrine pathways that regulate peripheral tissues that contribute to physical activity and energy expenditure. A classic example is 2,4-dinitrophenol, a mitochondrial uncoupler that promotes weight loss[92]. Rodents exposed to BPA as adults or to nicotine in the prenatal period had reduced physical activity and thermogenesis[93,94]. Exposure to pesticides such as chlorpyrifos, arsenic or DDT (Supplementary Table 2) decreased body heat without decreasing physical activity in mice[62,95,96].

The concept of a metabolic set point has been used to explain the long-term resistance to body weight change in response to calorie restriction. Altered metabolic set points favouring energy storage have been shown with exposure to TBT in mice[82] (Supplementary Table 2). In addition, decreased food efficiency (that is, the efficiency by which food is converted into body mass) favouring energy storage was observed in rats exposed to secondary stressors. For example, prenatal nicotine exposure decreased food efficiency in rats fed a high-fat diet[93], whereas a mixture of DDT and dichlorodiphenyldichloroethylene (DDE) decreased food efficiency when administered to adult rats under calorie restriction[97] (Supplementary Table 2).

Neuroendocrine pathways, such as β-adrenergic and thyroid hormone signalling, influence energy metabolism. β-Blockers, which are antagonists of β-adrenergic receptors, reduce resting energy expenditure in humans by approximately 5%; this effect seems to be independent of the reduced heart rate and difficulty achieving 'target heart rates' during physical activity[98]. Perchlorate disrupts thyroid hormone action by impairing thyroid hormone synthesis. This disruption causes decreased muscle heat production and suppression of lipolysis, findings that are consistent with associations linking human perchlorate exposure to diabetes mellitus and dyslipidaemia[99–102].

KC8: causes inappropriate nutrient handling and partitioning

Inappropriate nutrient handling and partitioning refers to the synthesis, release, transport, storage and breakdown of nutrients such as carbohydrates, lipids and amino acids. This process might result in T2DM or hypoglycaemia, dyslipidaemia, sarcopenia, or obesity and ectopic lipid deposition[15]. The mechanisms underlying alterations in lipid metabolism are complex and might be tissue-specific and sex-specific. Agents that induce abnormal lipid metabolism or deposition include glucocorticoids and antiretroviral drugs[14,103], light exposure at night[104] and environmental toxicants associated with dyslipidaemia[15], obesity[14,105] and MASLD (BPA, DEHP, TBT and triclosan)[106–109]. Glucose storage and mobilization are also affected by MDAs. Glucose storage as glycogen was reduced in the liver by exposure to BPA in pigs[110] and vinyl chloride in mice[111], and in shrimp muscle by exposure to organophosphorus insecticides[112] (Fig. 1). Conversely, glucose mobilization from glycogen

to prevent hypoglycaemia is impaired by some prescription antibiotics in people[113] and persistent organic pollutants in rats and mice[114–116]. Muscle is critical for postprandial glucose uptake and storage. Loss of lean mass is metabolically deleterious, and sarcopenia is linked with T2DM risk[117]. Reduced muscle mass is associated with HIV infection and some antiretrovirals[118,119], as well as glucocorticoids[120]. TBT induces muscle wasting and impaired muscle regeneration[121], whereas DDT and its metabolites adversely alter muscle health in mice[122].

KC9: promotes chronic inflammation and immune dysregulation in metabolic tissues

Chronic inflammation is a critical mediator of metabolic dysfunction that is associated with increasing adiposity (particularly in the visceral abdominal compartment) and the development of insulin resistance, which is a key feature of unhealthy obesity. Together, these alterations are referred to as metabolic inflammation[123,124] (Fig. 1). Efforts to identify how immunological cell types impair metabolic function in tissues revealed that pro-inflammatory cytokines and lipids have a role. Levels of several cytokines, both individually and in combination, including TNF, IL-6, IL-1β, IFNγ and PAI1, are elevated in tissues and systemically in individuals with metabolically unhealthy obesity[123,125,126]. These cytokines largely act via the NLRP3 inflammasome to link inflammation with obesity, insulin resistance and T2DM[22]. Macrophages can sequester substantial amounts of lipids present in tissues of individuals with obesity, and these foam cells are increasingly being implicated in fuelling the metabolic consequences of unhealthy obesity and unhealthy ageing in general[127]. Certain lipids can activate macrophages and other innate immune cell types, which are enriched in unhealthy weight gain[128]. These lipids include ceramides, phospholipids and saturated long-chain fatty acids. MDAs, including BPA, PCBs, TBT, DEHP, PBDEs, particulate matter with a diameter of 2.5 µm or less and the Western diet, have been shown in animal and human studies to be able to disrupt innate immunity and promote inflammation[129–132]. Therefore, dietary, chemical, toxic or pharmaceutical exposures could act as obesogens by potentiating metabolic inflammation by directly modulating the number or function of immune cell types, affecting their state of activation and cytokine secretion or modulating the balance between pro-inflammatory and anti-inflammatory lipid species.

KC10: disrupts gastrointestinal tract function

Specific gut functions that are critical to the maintenance of normal systemic metabolism and are susceptible to MDAs[14,105,133–135] include nutrient and water absorption, barrier function against pathogens and immune defence, as well as the production of gut-derived hormones that regulate systemic metabolism. Maintenance of microbial populations that generate health-promoting metabolites versus harmful products, as well as xenobiotic metabolism by the microbiome, are discussed in Box 3. MDAs can impair the normal intestinal barrier of microbiome-derived mediators through decreased intestinal mucus production, altered expression of epithelial tight junction proteins and antimicrobial peptide production (Fig. 1). Evidence for these effects is well-established for ethanol[136], and it has also been reported for various hypercaloric diets and environmental chemicals, including PCBs and dioxins in mice and humans[133,137]. MDAs, either endogenous or from the microbiome, can also disrupt gut-derived hormone production. For example, in mice low-level PCB exposures altered the microbiome composition by increasing the numbers of bile-acid-related bacterial species, which resulted in increased hepatic expression of the farnesoid X receptor (FXR) target *Cyp7a1* and altered primary and secondary bile acid production[138]. MDAs might regulate other gut hormones implicated in systemic metabolism. For instance, pharmaceutical GLP1 analogues have revolutionized the treatment of obesity and T2DM, whereas exposure to PCB126 reduced circulating levels of GLP1 in a mouse model[139]. Ghrelin (the gut-derived hunger hormone) increases food intake and was increased by exposure to the insecticide chlorpyrifos in rats, which also disrupted the gut microbiome, reducing diversity and shifting the composition to a more inflammatory-related profile[140]. Thus, MDAs might influence systemic metabolism by targeting the gut epithelium and the intestinal microbiome (Box 3). Other incretin targets, such as the glucose-dependent insulinotropic polypeptide receptor, can be targeted by pharmaceuticals[141] and, in principle, by MDAs.

KC11: induces cellular stress pathways

Oxidative stress is a contributor to the pathology of many disease states and is often considered by regulators in evaluating the potential toxicity of chemicals[142,143]. However, oxidative stress is also implicated

Box 3 | The role of the microbiome in producing KC10: disrupts gastrointestinal tract function

Metabolism-disrupting agents (MDAs) can affect gut function and microbial composition. It has been nearly two decades since Turnbaugh and colleagues first reported an obesity-associated gut microbiome with increased capacity for energy harvest[279]. This microbiome was characterized by an increased Firmicutes to Bacteroidetes ratio[279]. Since then, an altered intestinal microbiome has been associated with exposure to MDAs, including: fructose; non-nutritive sweeteners; ethanol; persistent organic pollutants, including polychlorinated biphenyls (PCBs), dioxins, perfluoroalkyl and polyfluoroalkyl substances and organochlorine insecticides; plasticizers, including bisphenol A and phthalates; metals, including arsenic, lead, cadmium and mercury; flame retardants; and numerous insecticides, herbicides, antifungals and antifouling agents, including tributyltin[105,134,135,280]. Several of these exposures, such as PCB126, have also been associated with obesity and an increased Firmicutes to Bacteroidetes ratio[279].

MDAs can influence the production of intestinal microbial metabolites (such as, indoles, bile acids, short-chain fatty acids and trimethylamine) and other gut-derived metabolites regulating systemic metabolism. Dietary tryptophan-derived indoles and their metabolites activate intestinal and hepatic aryl hydrocarbon receptors, to which certain PCBs, dioxins and furans also bind, to regulate inflammation and liver lipid metabolism[136]. Patients with severe alcoholic hepatitis and cirrhosis have an altered microbiome with decreased serum and/or faecal levels of tryptophan and/or its indole metabolites, which are predictive of 30-day mortality[280].

The microbiome can also participate in xenobiotic metabolism[281]. Digoxin is a prescription medication that is metabolized by a single gut microorganism, *Eggerthella lenta*. Colonization by this bacterium leads to decreased systemic levels of digoxin that are increased by oral antibiotics[281]. Therefore, a bi-directional interaction might exist between metabolism-disrupting xenobiotics and the gut microbiome.

as a key indicator of fuel excess[144]. Uncontrolled increased levels of reactive oxygen species (ROS) in adipocytes result in a net increase in triglyceride stores, and in pancreatic β-cells from rodents and humans, elevated levels of ROS cause increased insulin secretion[145] (Fig. 1). Redox reactants comprise an energy-responsive communication system within each cell and cellular compartment[144]. Metabolic stress produces ROS, oxidative stress, endoplasmic reticulum (ER) stress and mitochondrial damage. Protective survival-promoting responses to these stress stimuli primarily include the oxidative stress response and the ER unfolded protein response (UPR)[146]. Cellular stress or disruption of these ameliorating pathways by environmental agents alters cellular homeostasis and might change cell fate (see KC6). Metabolic diseases, such as MASLD, obesity and T2DM, are associated with oxidative stress resulting from mitochondrial dysfunction (see KC7). The relationships between mitochondrial dysfunction that produces elevated ROS, oxidative stress and ameliorating responses are well-documented in epidemiological studies of air pollution particulate matter of <2.5 µm in diameter, which is a known MDA[147]. ER stress resulting in increased ROS production from mitochondria is a common effect of chemical exposures. For example, AGRP-expressing mouse hypothalamic neurons (see KC3) undergo ER UPR in response to bisphenol S (a commercial replacement for BPA)[148]. The liver is a common target of stress; for example the pesticide atrazine increases both ER UPR and ROS in the liver of mice after impairing insulin and glucose tolerance[149]. Similarly, PFOA increased both ER UPR in mouse liver and human hepatocytes[150]. Furthermore, DEHP, BPA and PBDE-209 promote oxidative stress and increase ROS in the HEPG2 liver cell line[14,151–153] (Supplementary Table 2).

KC12: disrupts circadian rhythms

Energy metabolism responds to periods of feeding and fasting that occur with periodicity across the 24-h day. These circadian rhythms are entrained by light, influenced by food availability and synchronized at the organismal and cellular levels by molecular clocks. These clocks act centrally in the hypothalamus (central clock) and in the periphery (peripheral clocks), including in the tissues regulating energy metabolism[27,154] (Fig. 1). Diurnal rhythms of hormone secretion regulated by the central clock synchronize the peripheral clocks and regulate multiple aspects of metabolism, including sleep–wake cycles, appetite versus satiety and energy expenditure[155]. The circadian disruption caused when the clocks misalign (including jet lag and shift work) induces metabolic dysfunction (Fig. 1). Sleep disruption, by itself or as a result of circadian disturbances, also promotes metabolic dysfunction[156]. Several pharmacological agents associated with metabolic dysfunction alter circadian biology and/or sleep. These include glucocorticoids[157], β-blockers[158,159], paroxetine[160,161], amitriptyline[162], clozapine[163,164] and olanzapine[163,164]. Physical agents that disrupt circadian biology and promote metabolic dysfunction include increased levels of noise[165–169] and light exposure at night (that is, inappropriate exposure to light during typical periods of darkness)[170,171]. Chemical agents that disrupt aspects of circadian rhythms or clock biology include tolylfluanid[172], arsenic[173], PCBs[174] and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin[175].

Examples of MDAs with one or more KC

In this section, we illustrate how a series of well-known MDAs are objectively known to have one or more of the 12 KCs outlined in the previous section. We provide this evidence for three pharmacological agents (that is, glucocorticoids, streptozotocin and AAPs) and three environmental agents (BPA, DDT and TBT), as well as for an infectious agent (hepatitis C virus; Box 4). Although most of these example MDAs have substantial evidence supporting most to all of the KCs, streptozotocin is unique in that it has strong supporting evidence for only one KC. This feature highlights that the number of KCs associated with a specific agent does not predict that an agent will be an MDA but rather indicates that it is the strength of the evidence supporting one or more KCs that is important in the identification of an MDA.

Box 4 | Hepatitis C virus has numerous key characteristics of metabolism-disrupting agents

Hepatitis C virus (HCV) is a leading cause of cirrhosis and liver cancer worldwide. HCV infection can be readily cured by potent directly active antiviral agents. HCV also has several key characteristics (KCs) of a metabolism-disrupting agent (MDA). HCV promotes insulin resistance (KC4) within hepatocytes. Indeed, insulin resistance and diabetes mellitus are extrahepatic manifestations of chronic HCV infection. HCV core protein reduces phosphoinositide 3-kinase and AKT signalling by abnormally phosphorylating IRS1 and/or IRS2 via both direct and indirect (via upregulated cytokines and their regulator proteins) mechanisms[282]. HCV NS5A protein leads to reduced forkhead box protein O1 phosphorylation, and HCV downregulates the glucose transporter GLUT2 (ref. 282). Cure of HCV infection is associated with improved insulin resistance and decreased incidence of hyperglycaemia and diabetes mellitus[283]. Reduced insulin requirements have resulted in hypoglycaemia in some patients who did not reduce their usual insulin dose after HCV cure.

HCV causes inappropriate nutrient handling and partitioning (KC8). HCV circulates as a lipid-rich particle and utilizes cell surface receptors for lipoproteins to gain entry into hepatocytes. Not surprisingly, HCV causes abnormal lipid partitioning with increased hepatic steatosis accompanied by reduced circulating levels of VLDL cholesterol[283]. In hepatocytes, HCV upregulates lipid synthesis while reducing mitochondrial β-oxidation and VLDL secretion[283]. For example, HCV core protein can reduce the activity of the microsomal triglyceride transfer protein required for VLDL biosynthesis in hepatocytes. Following HCV cure, reversal of hepatic steatosis and increased circulating levels of cholesterol have been found in some studies. Importantly, some patients who did not require lipid-lowering medications before treatment might require them after treatment. Although debated in the literature, cardiovascular risk might decrease following HCV cure, despite the observed risk of post-treatment dyslipidaemia[283].

HCV promotes chronic inflammation and immune dysregulation in metabolic tissues (KC9). Liver inflammation and fibrosis are hallmarks of chronic HCV infection that improve after cure. Finally, HCV induces cellular stress pathways within the liver (KC11), including mitochondrial dysfunction and oxidative stress. Chronic HCV infection exhibits several KCs of an MDA. Although HCV-associated hepatic insulin resistance, steatosis and inflammation tend to improve with viral cure, blood levels of lipids might worsen. This example shows that the KCs described in this article can be applied to all forms of causative agents, including infectious agents.

Examples of pharmacological agents with specific KCs

Glucocorticoids. Pharmacological glucocorticoids are characterized by their ability to activate glucocorticoid receptor signalling. Glucocorticoid receptor signalling disrupts many aspects of metabolic physiology. Supplementary Table 1 summarizes the many metabolic effects of glucocorticoid excess, including those arising from pharmacological glucocorticoid treatment[176–179]. Although the specific metabolic effect of pharmacological glucocorticoids on metabolism in any individual varies based on drug potency, dose, duration and route of administration, pharmacological glucocorticoids have multiple KCs of MDAs; for instance: impairments of in vitro and in vivo insulin secretion by pancreatic β-cells in rodents[180] (KC1); alterations in white, beige and brown adipose physiology in rodents[181–183] (KC2); and alterations in metabolic signalling in the brain, control of appetite and central regulation of peripheral metabolism in rats[184–186] (KC3). Classically, glucocorticoids induce whole-body[187,188] and tissue-specific[179] insulin resistance in humans (KC4). The dysregulated activation of glucocorticoid receptor signalling largely drives these adverse effects; however, secondary glucocorticoid-mediated signalling effects and crosstalk via insulin, sex steroids and osteocalcin are recognized[189,190] (KC5). Glucocorticoid receptor signalling is critical in adipocyte differentiation, whereas excess signalling through this pathway can promote β-cell apoptosis[191] (KC6). Consistent with their effects on brown and beige adipose tissue, glucocorticoids also impair energy expenditure[182] (KC7). At the cellular and tissue levels, excess glucocorticoid receptor signalling increases hepatic gluconeogenesis, lipogenesis, lipid uptake and steatosis, and promotes impairments in nutrient uptake and storage in muscle[179,192,193] (KC8). Although glucocorticoids are used for their anti-inflammatory properties, they can increase macrophage infiltration of adipose tissue in mice[194] (KC9). Glucocorticoids modulate intestinal permeability and are commonly used to treat inflammatory bowel diseases; they might also alter the gut microbiome in mice[195,196] (KC10). At the cellular level, glucocorticoids can induce ER stress in rats[191] and promote lipotoxic effects on pancreatic β-cells in humans[197] (KC11). Finally, pharmacological glucocorticoids can disrupt the typical endogenous circadian rhythm of glucocorticoid receptor signalling and alter sleep in people[157] (KC12).

Streptozotocin. In contrast to glucocorticoids, which show multiple KCs, streptozotocin has only one KC. Streptozotocin is an anticancer agent that is approved by the FDA for the treatment of metastatic islet cell carcinoma of the pancreas, and has a profound capacity to alter metabolism through its selective toxicity on pancreatic β-cells[198] (Supplementary Table 1). The chemical structure of streptozotocin augments its targeted uptake in β-cells via the glucose transporter 2 (GLUT2)[199,200], where its alkylating properties induce cell death[201]. The consequence of this β-cell toxicity is the induction of hyperglycaemia and diabetes mellitus in animal models and in some patients being treated for metastatic islet tumours[202–204]. Indeed, streptozotocin is now frequently used as a tool to generate experimental models of diabetes mellitus. Although the therapeutic purpose of streptozotocin is to treat metastatic islet cell carcinomas, its capacity to induce a diabetic state through the selective destruction of pancreatic β-cells demonstrates how a pharmacological agent with strong evidence of only one KC of an MDA (KC1) is sufficient to drive severe metabolic dysfunction.

AAP medications. AAP medications include anti-dopaminergic agents with varying capacities to antagonize noradrenaline and serotonin signalling. Including such agents as olanzapine, clozapine, aripiprazole, risperidone and ziprasidone, and others, AAPs are indicated for the treatment of bipolar I disorder, bipolar depression, schizophrenia and schizoaffective disorders, as well as adjuncts in the treatment of major depressive disorder[205]. Although there are drug-specific differences in the capacity of various AAPs to disrupt metabolism, as a class, their use is associated with multiple metabolic disturbances and KCs of metabolism disruptors[64–67] (Supplementary Table 1). In vitro studies showed that clozapine increased basal insulin secretion in rat cells[206] (KC1), whereas olanzapine altered white adipose tissue physiology in rats[207] (KC2). Consistent with their clinical purpose of modulating neuronal function to alleviate the symptoms of psychiatric disorders, AAPs can alter multiple central pathways that regulate energy metabolism (KC3). AAPs modulate body weight via several routes: by interaction with histaminergic receptors, particularly H1 in rodents and humans[208]; by interaction with specific serotonergic receptors (depending on single nucleotide polymorphisms)[209]; and by effects on hypothalamic neuropeptide signalling in rats[210]. AAPs are associated with tissue-specific and global insulin resistance in humans and rats[207,211] (KC4). Multiple signalling molecules involved in metabolic regulation are altered by AAPs, including prolactin in humans[212] and catecholamines in rodents[213] (KC5). Clozapine can promote adipocyte differentiation from human adipose progenitors[214] (KC6) and altered energy homeostasis in humans[215] (KC7). Robust evidence links AAPs to alterations in nutrient handling and partitioning (KC8), including hyperglycaemia, glucose intolerance, increased diabetes mellitus risk, hepatic steatosis, altered circulating profiles of lipids and increased adipose mass, especially in the visceral compartment. Studies in rodents have suggested that this adipose expansion is accompanied by macrophage infiltration[216] (KC9). AAPs are implicated in altered intestinal physiology, which facilitates dietary lipid absorption in mice and cultured human intestinal cells[217], as well as alterations in the gut microbiome in rats[216] (KC10). Some data indicate that olanzapine might alter mitochondrial function in rodents[218] (KC11). Finally, AAPs can alter circadian patterns of hormone secretion that are linked to metabolic function, including cortisol and growth hormone in humans[219,220] (KC12). Although the effects of AAPs on metabolic physiology probably vary based on drug, dose, duration of treatment and underlying susceptibility, as a class, AAPs exhibit multiple KCs of MDAs.

Examples of environmental agents with specific KCs

BPA. Systematic reviews and meta-analyses have identified a notable association between BPA exposure and the prevalence of T2DM[221]. Increased urinary levels of BPA are associated with hyperinsulinaemia, insulin resistance[222] and increased levels of HbA_{1c}[223]. A meta-analysis[224] and a case–control study[225] linked BPA exposure with obesity in adults, whereas cross-sectional studies associated BPA with obesity in children and adolescents[226]. Abundant evidence in animal models demonstrate that BPA exposure elicits variations in metabolic phenotypes that are dependent on exposure time, treatment doses, sex and age, with the period of greatest susceptibility during pregnancy[227] (Supplementary Table 2). Developmental exposure causes weight gain (KC8), insulin resistance (KC4), glucose intolerance (KC8), hyperinsulinaemia (KC1), altered β-cell mass (KC6), increased hepatic levels of triglycerides (KC8) and increased inflammation (KC9)[14,228–230], together with metabolome changes[231] and hepatic transcriptome reprogramming[232]. BPA disrupts colonic permeability and alters the gut microbiome[233,234] (KC10). Although results point to the autonomic[110] and central[235,236] nervous systems as possible BPA targets (KC3), alteration in nervous system control requires further study. BPA modifies the secretion-stimulus coupling mechanism[237] and increases insulin secretion in human β-cells[238], rodent β-cells and β-cell lines[227] (KC1). BPA action involves nuclear receptors[237,239]

and apoptosis-associated ROS production[239] (KC11). In adipocytes, BPA induces adipogenesis (KC6), disrupts adipocyte function (KC2)[240,241], alters insulin signalling (KC4) and causes inflammation[225]. In liver cell lines, BPA produced triglyceride accumulation and steatosis (KC8)[242,243]. Thus, BPA has multiple KCs of an MDA.

DDT and DDE. Numerous meta-analyses of prospective epidemiology studies have demonstrated a positive association between DDE and obesity[244,245]. Most of this evidence is largely for prenatal DDE exposure and childhood obesity. There are also prospective studies that have revealed a positive association between DDT exposure during pregnancy and obesity in teenaged and middle-aged offspring as well as granddaughters in their twenties[246,247]. Meta-analyses of mostly cross-sectional epidemiology studies have also demonstrated a positive association between DDE and diabetes mellitus[248]. A few cross-sectional human studies have demonstrated a positive association between DDT and hepatic lipid content and MASLD[249].

In rodents, DDT is known to be metabolized to DDE; however, if only DDT was dosed, we refer to that exposure as DDT for clarity. Prenatal DDT exposure causes increased adiposity in mouse offspring, and DDT exposure during pregnancy causes increased adiposity in subsequent generations of rats (generations two and three) via epigenetic transgenerational inheritence[62,250]. These DDT doses resulted in levels of DDT and DDE within the range of prospective epidemiology studies in one of the meta-analyses of obesity[244]. In other rodent studies, DDE exposure during adulthood had no effect on body weight gain, but induced hyperglycaemia in mice (or adiposity when exposure was in adulthood)[251]. Prenatal DDT exposure impaired glucose tolerance and elevated fasting and fed insulin levels in rodents (KC4)[62,252]. Prenatal DDT exposure also reduced energy expenditure (KC7), body temperature, cold tolerance, brown adipose innervation and sympathetic ganglia dendritic density in adult mice (KCs 3 and 7)[62,253] (Supplementary Table 2). Adult rats exposed to DDE and DDT also had reduced body temperature (KC7) and disrupted thyroid-stimulating hormone levels[97] (KC5). These in vivo findings in numerous mammalian species might be related to decreased mitochondrial oxidative phosphorylation when exposed to DDT or DDE (KC11)[254].

DDT increased adipogenesis in cultured adipocytes; however, this effect was less consistent with DDE[244]. Nonetheless, DDT and DDE both dose-dependently decreased insulin-stimulated glucose uptake in adipocytes[255] (KC2, 4 and 8). There was also reduced pancreatic β-cell area (KC6) and glucose-stimulated insulin secretion (KC1) in several generations of rats after maternal DDE exposure accompanied by transgenerational DNA hypomethylation of *Igf2* and *H19* in the islets[252]. A systematic review revealed that DDT increased hepatic levels of cholesterol and triglyceride across numerous experimental studies in rats (KC8), which was not seen in mice or on DDE exposure[244]. By contrast, there is stronger evidence for DDE than for DDT with respect to the numbers of studies and species studied in shifting the composition of the gut microbiome to a pro-obesity state (KC10)[256].

TBT. There are few human studies linking TBT with adverse outcomes, mainly because it is difficult to measure accurately. TBT and other organotins are found at bioactive levels in human blood and tissues, seafood, certain foods and house dust[257–264]. Studies in rodents have demonstrated that low doses of TBT can lead to adipose tissue accumulation and obesity, particularly if the animals are also challenged with increased dietary fat[14]. These effects can be manifested across multiple generations without further exposure (KC6)[82,85]. TBT also induces adipose accumulation in fish[14]. Nearly 500 mechanistic scientific papers on TBT provide substantial evidence for all 12 KCs described in this article (Supplementary Table 2). Experimental studies have revealed that TBT binds to and activates multiple nuclear hormone receptors, including RXR, an obligate heterodimeric partner in multiple metabolic signalling pathways regulated by PPARs, liver X receptors, thyroid hormone receptors, FXR and PXR[14] (KC5). TBT also promotes production of inflammatory cytokines such as IL-1β and IL-6 (ref. 265) (KC9). TBT exposure altered H3K27 trimethylation in cultured MSCs, diverting them to the adipose fate[266] (KC6). Gestational TBT exposure in rodents led to changes in higher-order chromatin structure, producing a predisposition to diet-induced hyperinsulinaemia, insulin resistance, MASLD and obesity[83] (KC4).

Conclusions and recommendations

We conclude that the KCs described here could be used extensively in the further development of the metabolism disruptor field. To date, metabolic disruption has not been emphasized in testing or risk assessments of environmental or pharmaceutical agents. Identifying novel MDAs clearly should be a priority, especially for occupational and environmental chemicals, as more than 41.4% of adults in the USA now have obesity[267]. Obesity is linked with multiple comorbidities, including cardiovascular disease, MASLD, dyslipidaemia, hypertension, T2DM, death from COVID-19 and at least 13 types of cancer[18]. The economic costs to health care and public health practices in the USA alone are huge. Obesity adds more than US $170 billion annually to adult health-care costs and another US $116 billion to child health-care costs in the USA[268]. The total annual cost of diabetes mellitus is nearly US $413 billion; indeed, one in four US health-care dollars is spent on costs associated with diagnosed cases of diabetes mellitus[269].

Despite this high societal burden, there is no current basis to systematically investigate metabolism-disrupting activity or to support evidence-based classification as MDAs. The KCs of MDAs are introduced to bridge this important gap. As with other KCs, the KCs of MDAs discussed here are inherent properties of the disruptive agents themselves and address the major mechanisms through which metabolic processes can be disrupted. A critical point is that these KCs are agnostic towards any particular adverse outcome pathway, as nearly all of these disruptive agents target multiple pathways and end points (Box 2; Supplementary Tables 1 and 2). Because of their direct relevance to human MDAs, we propose that the KCs identified here can be leveraged in several ways.

1. The KCs for MDAs described here provide a useful framework as the basis for developing hazard identification and risk assessment for MDAs, which will become an important cornerstone for regulating chemicals based on their metabolism-disrupting properties.
2. Specifically, we recommend that the 12 KCs for MDAs elaborated here be used as a basis of systematic evidence reviews to establish the biological plausibility of a metabolism-disrupting effect occurring in humans, similar to how the KCs for carcinogens are used by various authoritative bodies. Under the framework that is typically used, the strength of the mechanistic evidence for each KC is determined and can be used, if needed, to develop a probable mode of action or otherwise support hazard identification. This stepwise evaluation involves several steps: expert review of the mechanistic studies relevant to each KC; synthesis of evidence across all KCs; and finally, evidence integration or triangulation together with the human epidemiological and experimental animal data on apical end points (see the IARC

Preamble[5], as one example). Using this framework, it would be possible to reach an overall hazard classification for MDAs, indicating that the agent is an MDA in humans or falls into a lower risk category (that is, it is probably or possibly an MDA in humans, or is not classifiable).

3. In 2023, the National Academies in the USA recommended that the Environmental Protection Agency adopt a hazard identification framework that does not require epidemiological studies in humans or laboratory studies in mammals, similar to IARC's approach for evaluating carcinogens[270]. In line with this recommendation, the KCs of MDAs on their own could support a conclusion that a substance is a possible MDA. The KCs of MDAs could also strengthen conclusions based on apical end points from epidemiological studies in humans or laboratory studies in animals by supporting biological plausibility.
4. We further recommend that the 12 KCs of MDAs described here should be used to identify priorities for assay development and validation for future regulatory use. Cataloguing the existing in vitro and in vivo assays relevant to KCs of MDAs routinely used by the scientific community and developing best practices is warranted, similar to those used by the NIDDK Mouse Metabolic Phenotyping Centers[271].
5. Although informative individually, the KCs could also support designing and conducting a battery of tests to explore various MDA activities more broadly. Assays relevant to the KCs of MDAs have utility in various settings, such as high-throughput in vitro screening to prioritize agents for further testing, as well as for exploring specific mechanistic hypotheses in human populations, in mammalian models or with new approach methods.
6. As illustrated, most chemicals have more than one KC, and some might even have all 12 (such as, TBT). In principle, the effects of an agent having more than one KC could be additive or antagonistic. This feature would be identified as part of expert analysis in developing a weight of evidence approach to the hazards associated with any particular chemical. Furthermore, knowing whether an agent had more than one KC could inform assay development aimed at prioritizing agents for additional analysis.

In summary, this Consensus Statement presents 12 KCs of MDAs and highlights the evidence that supports the identification of these KCs. We use chemical, infectious and physical agents as examples to illustrate how the KCs can be used to organize and use mechanistic data to help to identify MDAs. We propose that the KCs of MDAs provide a basis to systematically investigate metabolism-disrupting activity. They could support hazard identification, risk assessment and the classification of potential MDAs in humans, and help to prioritize assay development for MDA identification.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

M.T.S. has served as a paid consultant and expert witness in litigation involving chemical and pharmaceutical exposures and various disease outcomes that are unrelated to the present manuscript. M.T.S. is president and CEO of 1Tox and also conducts research in areas of interest similar to the business interests of 1Tox. R.M.S. declares he has received honoraria from CVS/Health that are unrelated to the present work. M.C.C. received research support and/or

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Additional information

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