Hormesis and public health: can glutathione depletion and mitochondrial dysfunction due to very low-dose chronic exposure to persistent organic pollutants be mitigated?

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ABSTRACT

Background Exposure to persistent organic pollutants (POPs) is linked to many chronic diseases, including diabetes and cardiovascular diseases. Among several possible mechanisms are gradual glutathione depletion and mitochondrial dysfunction after chronic exposure to very low doses of POP mixtures. However, it is biologically noteworthy that glutathione status and mitochondrial function is subject to hormesis, defined broadly as mild stress-induced stimulation of cellular protective mechanisms, including increased synthesis of glutathione and promotion of mitochondrial biogenesis. Although high levels of reactive oxygen/nitrogen species (ROS) can cause cellular damage, certain levels of ROS function as signalling molecules to induce hormetic effects. Thus, similar to many other stressors generating ROS, glutathione status and mitochondrial function can be improved at higher POP doses. However, higher POP levels are dangerous despite their hormetic effects due to other adverse phenomena. Also, the persistent nature of POPs can make hormetic effects less effective in humans as hormesis may be the most active with transient stressors. Hormesis-inducing stressors should be placed into three categories for public health purposes: (1) disadvantageous: chemicals like POPs and radiation, that could harm humans by endocrine disruption, action of chemical mixtures and susceptible populations; (2) neutral: cold, heat, and gravity; and (3) advantageous: moderate exercise, phytochemical intake, and calorie restriction. Noting that regulation of POPs, while critical, has provided insufficient protection because POPs persist in human bodies and the food chain, advantageous stressors should be used by the public to mitigate glutathione depletion and mitochondrial dysfunction due to POPs.

INTRODUCTION

Recently, background environmental exposure of the general population to persistent organic pollutants (POPs) has been linked to a variety of chronic diseases including type 2 diabetes and cardiovascular diseases.[1–5] Considering that the most problematic chlorinated POPs were banned several decades ago and that the exposure levels of people now are much lower than of people in the 1960s and 1970s,[6] it may be surprising that this human evidence is just starting to come to light.

POPs is a general term for the mixture of several hundred or thousand chemicals with common properties including strong lipophilicity, resistance to biodegradation and biomagnification in the food chain.[7] Although toxicological and epidemiological studies traditionally have tried to identify which specific POPs cause harm, the disease risk associated with serum POP concentrations is better thought of as reflecting POP mixtures.[5]

The primary approach to protecting the public against chemical exposure is by avoiding them through regulation of individual chemicals, including banning, strict safety standards and carefully controlled use. While regulation is critical, it has not fully protected against POP mixtures, for several reasons. First, the most problematic chlorinated POPs have already been banned and strictly regulated in many countries, but that has not eliminated exposure to POPs.[8] Second, POPs have thoroughly contaminated our food chain during the 20th century. At present, fatty animal foods are the main external human exposure source of various POP mixtures.[9] Third, POP mixtures already in body stores are continuously released to circulation from adipose tissue along with physiological fat mobilisation.

Given these structural insufficiencies in avoidance of POPs through regulation, policy or law, a deeper understanding of the biology involved with POPs may be helpful to counteract harmful effects of low-dose POPs. The dose we discuss here is very low, not enough to induce any biologically meaningful chemical-specific response and often omitted from experimental animal studies. Thus, we will use the term 'very low dose POPs mixture' for this range of dose. Also, the exposure duration of concern is chronic exposure, sometimes lifetime, which is rarely considered in in vitro and in vivo experimental settings either. Our thesis is that the chronic exposure to very low dose POP mixtures is sufficient to cause glutathione depletion and mitochondrial dysfunction, which can be mitigated by stress-induced stimulation of these body systems, particularly using safe, lifestyle-related stressors.

GLUTATHIONE DEPLETION DUE TO CHRONIC EXPOSURE TO VERY LOW DOSE POPS

All living organisms have normal physiological mechanisms to facilitate excretion of unwanted exogenous or endogenous chemicals through biotransformation, conjugation and transport.[10] Among many conjugators, conjugate derivatives of glutathione (GSH) are major excretion products of POPs such as polychlorinated biphenyls (PCBs) and organochlorine pesticides.[11–15] Also, some compounds like dichlorodiphenyltrichloroethane (DDT)

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requires GSH for dehydrochlorination.[14–16] Thus, long-term exposure to POPs can continuously consume GSH. In the case of POPs, the situation is worsened by intestinal reabsorption. The main excretion route of POPs is faeces, unlike other common chemicals that are mainly excreted in urine and a substantial portion of POPs excreted in bile is reabsorbed by the intestine after deconjugation by intestinal microflora.[17] Reabsorption of bile and other compounds returning to the liver is called 'enterohepatic circulation'.[18] This mechanism can lead to a viscous cycle of consumption of GSH.

Unless there is a compensatory mechanism like increased synthesis of GSH, the continuous consumption of GSH through POP metabolism can lead to chronic GSH depletion. Besides its role in excretion of chemicals, GSH is a key biomolecule in maintenance of redox status of the cell.[19] Depletion of GSH can cause various harmful biological effects in relation to imbalance of redox status. Therefore, even though individual POPs at very low dose may not generate oxidative stress sufficient to affect cell functions, long-term exposure to POP mixtures at very low dose may adversely affect intracellular oxidative balance indirectly through intracellular GSH depletion. It is important to note that GSH depletion due to chronic exposure to POP mixtures at very low doses happens as a result of adaptational mechanisms in living organisms against xenobiotic chemicals, even when there is no POP-specific biological response.

Chronic exposure to very low dose chemical mixtures has not received much attention in traditional animal experimental studies. However, supporting our hypothesis, one animal study evaluated how POP dose and exposure duration could affect GSH levels. In that study,[20] GSH contents were measured in various organs of mice after treatment over a broad range (0.15–150 ng/kg/day) of doses of 2,3,7,8-tetrachlorodibenzodioxin (TCDD), which is a specific POP. Compared to control mice, very low dose exposure to TCDD (0.15 ng/kg/day) for 13 weeks, which was estimated to be similar to current human background exposure, led to GSH depletion in liver, kidney and lung. However, GSH contents started to increase with increasing doses of TCDD. On the other hand, acute exposure did not deplete GSH contents at any dose and GSH levels increased only with higher doses of TCDD. This finding suggests that only the chronic exposure to very low dose TCDD can cause GSH depletion and that there are compensatory pathways to increase GSH synthesis with increasing dose of TCDD which will be discussed below.

A GAP BETWEEN LABORATORY RESEARCH AND THE REAL WORLD: THE REASON FOR GLUTATHIONE DEPLETION IS IMPORTANT

As GSH is a key biomolecule, investigation of biological effects of GSH depletion is a very important topic for laboratory research. In experimental settings, GSH depletion is usually induced by treatment with selective inhibitors of GSH synthesis, in particular γ-glutamylcysteine synthetase.[21] Although researchers know that treatment with certain chemicals can induce GSH depletion through GSH consumption, this design is not preferred by laboratory researchers who want to evaluate biological effects due to absolutely low GSH. This is because outcomes of GSH depletion after chemical treatment reflect both GSH depletion and chemical exposure, not the pure biological effects of absolutely low GSH levels.[21]

However, how GSH depletes is important for understanding the true nature of GSH depletion in living organisms. Mutation of enzymes regulating GSH synthesis can cause GSH depletion in humans; however, considering the critical roles of GSH in life, it is highly plausible that fetuses with serious GSH synthesis defects abort spontaneously. In this logic, GSH depletion due to the exposure to chemicals may be more common in chemical-contaminated modern societies than are genetic GSH synthesis defects. Also, biological outcomes accompanying GSH depletion due to chemical exposure include possible further harmful effects of the chemicals themselves, beyond GSH depletion by inhibition of GSH synthesis, as laboratory researchers have already recognised.[21]

POP MIXTURES AND MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction has been proposed as a key cause of aging and aging-related diseases.[22] It can cause a wide range of seemingly unrelated diseases including diabetes, coronary heart disease, neurodegenerative diseases, and cancer because mitochondria convert the energy of food molecules into the adenosine triphosphate (ATP) that powers most cell functions.[22] There is substantial toxicological evidence that a variety of environmental chemicals including POPs can damage mitochondria.[23] However, most such evidence points to direct damage to mitochondria after high-dose exposure to individual chemicals in doses close to toxicity levels. Thus, their findings may not be applied to humans with very low dose exposure to chemical mixtures.

On the other hand, a recent animal study demonstrated that subchronic exposure to very low dose POP mixtures can induce mitochondrial dysfunction.[24] In this experimental study, rats were treated with a POP mixture contained in fish oil, mimicking the main POP exposure source in humans. The body burden of POPs in the experimental animals was similar to that of adults in current Northern European populations.[25] Therefore, we can assume that their experimental condition very likely mimicked the human situation in terms of exposure pattern. There were no clear change in mitochondrial DNA contents in the liver of rats fed a high fat diet contaminated with POPs, but gene expression profiles showed significantly reduced expression of several genes related to mitochondrial function such as PGC1α, citrate synthase, medium–chain acyl CoA dehydrogenase and succinate dehydrogenase, compared to those with high fat diet using fish oil that had been decontaminated to remove POPs.[24] These findings suggest that chronic exposure to very low dose POP mixtures can induce the impairment of mitochondrial function.

That study[24] did not assess whether mitochondrial dysfunction was the result of direct damage by the very low dose POP mixture or indirect effect due to GSH depletion. However, mitochondrial function can be influenced by an indirect pathway such as chronic GSH depletion which can be caused by the combination of 'very low dose' and 'chronic' exposure to POPs. In fact, the mitochondria are highly sensitive to intracellular GSH depletion.[26] Even though mitochondria are the primary site of generation of reactive oxygen/nitrogen species (ROS), they cannot synthesise GSH; rather they utilise intracellular GSH. ROS like superoxide anion and hydrogen peroxide continuously leak from the electron transport system of mitochondria; protection against the resultant oxidative stress mainly depends on GSH peroxidase and non-enzymatic reactions with GSH.[26]

At present, there is no direct experimental evidence about pathways linking chronic exposure to very low dose POP mixtures, GSH depletion and mitochondrial dysfunction. However, evidence from normal physiology, metabolism of POPs, and some toxicological studies on very low dose TCDD and low dose POP mixtures strongly supports our hypothesis. Although in vitro and in vivo experimental studies can sometimes be

helpful to understand molecular mechanisms, the scope of hypotheses which can be directly tested in experimental settings is practically limited. A comprehensive approach and insightful study design would be needed to infer biological effects of very low dose chronic exposure to POP mixtures in complicated and interconnected systems operating in living organisms.

CAN WE COUNTERACT VERY LOW DOSE POP MIXTURES?

When a certain chemical is known to be potentially harmful in humans, the first step an individual can take to reduce exposure is to avoid known exposure sources. Therefore, existing regulation that attempts to control POP exposure is critical. On a personal level, avoidance of highly POPs-contaminated food like fatty animal food is one way to avoid further exposure to these chemicals. However, the direct avoidance of POPs exposure from food may have limited effects because adipose tissue already stores substantial amounts of POPs. Therefore, another strategy to decrease body burden of POPs is to block enterohepatic circulation of POPs excreted in bile; this strategy would decrease the half-lives of POPs. Dietary fibre, non-absorbable lipids like olestra, or bile acid resins like cholestyramine reportedly have the ability to absorb POPs in bile and increase their excretion via faeces.[27–30] Both strategies, avoidance of fatty animal food and blocking enterohepatic circulation, are important in decreasing body burden of POPs in the long term.

Another protective strategy might be to combat GSH depletion and mitochondrial dysfunction, given that they are likely key mechanisms of risk for many diseases after chronic exposure to POP mixtures. Unlike the methods to decrease body burden of POPs, any methods that combat GSH depletion and mitochondrial dysfunction could exert fast responses because of direct action on molecular pathways.

NON-MONOTONIC DOSE–RESPONSE RELATIONSHIPS

Before jumping into ways to counteract harmful effects of very low dose POP mixtures on GSH depletion and mitochondrial dysfunction, we turn to a detailed discussion of the dose–response relationship which POP mixtures have shown in human studies. One puzzling epidemiological finding on POPs has been that harmful effects seemed to emerge in the very low dose POPs range, with little further increase in risk with increasing POPs doses.[5] In some studies, there was even a tendency for decreasing risk of diseases with increasing POPs dose, making an inverted U-shaped association.[31 32] These findings go against the conventional toxicological paradigm, in which harmfulness from chemicals increased with increasing chemical dose.

Recently, the possibility of non-monotonic dose–responses of chemicals has received attention.[33 34] To the extent that non-monotonic dose–responses prevail, the current policy on chemicals based on traditional risk assessment with the linearity assumption is highly questionable. The most discussed molecular mechanism explaining non-monotonic dose–response relationships is endocrine-disrupting properties of chemicals.[33] Endocrine-disrupting chemicals can have biological effects at low doses that are not observed at higher doses, because these chemicals follow the same biological rules as natural hormones, which also often display various non-monotonic dose–response relations.[33] Another molecular mechanism is hormesis, in which the non-monotonic dose–response relations take particular forms.[35] The classical example of hormesis is biphasic dose–response relationships of chemical stressors that are beneficial at a low level but harmful at a higher level, commonly characterised by a biphasic dose response.[35] Molecular mechanisms of hormetic dose/concentration response for endogenous and exogenous compounds were extensively reviewed in one recent article.[36]

Although both endocrine disruption and hormesis are ways in which low doses can have impacts that cannot be predicted from high-dose conventional experiments, their practical implications are completely opposite. In an endocrine-disrupting mechanism, low dose can be more harmful than high dose. Thus, endocrine-disruption researchers state that exposure doses below current safety levels are never safe and that the safety limit should be greatly lowered or the chemical should be banned in some cases.[33] On the contrary, in the case of hormesis, low dose can be beneficial compared to non-exposure, even though high dose is harmful.[35] Hormetic effects of chemicals have been a topic of vigorous debate because hormesis-advocating researchers suggest changing health policies to permit higher exposures of chemicals in humans.[37 38] This seems to be a risky strategy for chemicals that have known adverse effects and whose exposure levels are not controllable at the individual or the population level.[37 38]

Recent human studies which linked background POPs exposure to various diseases in the general population[1–5] suggest the existence of low dose harmful effects, not low dose beneficial effects. At first glance, thus, this phenomenon seems to be related to endocrine-disrupting mechanisms, rather than hormesis. However, understanding of human findings about effects of POPs can be enhanced by referring to hormesis, because hormesis is a good fit to the molecular mechanisms of GSH depletion and mitochondrial dysfunction we discussed above.

Compared to of GSH depletion and mitochondrial dysfunction, biological net effects due to endocrine-disrupting mechanisms are very difficult to characterise in the situation of chemical mixtures. Many experimental studies of individual chemicals have shown certain types of non-monotonic dose–response relations through endocrine disrupting mechanisms.[33] However, humans are simultaneously exposed to a huge number of chemicals that can function as antagonists or agonists to many endogenous hormones through direct and indirect pathways. As a typical example of chemical mixtures, POPs include compounds with various endocrine-disrupting properties including oestrogenic, antioestrogenic, antiandrogenic and thyroid-like activities.[39–42] Of importance, biological effects of one endocrine-disrupting chemical can differ greatly depending on the presence of another endocrine-disrupting chemical.[43–45] Thus, it is difficult to predict what kind of synergistic, additive or antagonistic actions of POPs mixtures occur.

ANOTHER GAP BETWEEN LABORATORY RESEARCH AND THE REAL WORLD: EXPOSURE RANGES AND DURATIONS ARE IMPORTANT

In the traditional hormetic dose–response relationship, possible beneficial effects in a dose range lower than toxicity levels are contrasted with possible harmful effects in the toxicity range.[46 47] Human findings about POPs demonstrated a harmful zone in the very low dose ranges of POPs and this harm did not clearly increase or sometimes decreased as dose increased. Therefore, the POP dose–response relationship in humans, while non-monotonic, can look different from the traditional hormetic curve. However, this discrepancy occurs due to differences in the range of exposure doses between experimental animal and human studies.

It is important to note that a possible harmful zone for very low dose POPs has not been properly examined in experimental animal studies of chemicals, even in studies focusing on hormetic effects of chemicals. In such a study, dose should be very

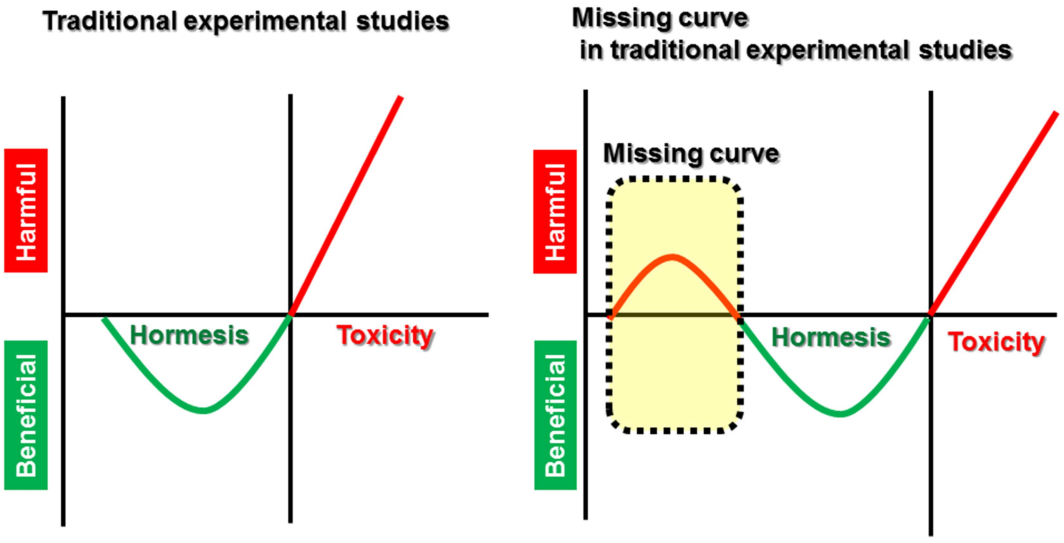

Figure 1 A possible harmful zone for some chemicals at a very low dose is not generally included in experimental animal studies. Conventional designs include only several dose points over a very wide range including a non-exposure control group. Study of this postulated harmful zone requires an even lower dose, not sufficient to induce hormetic responses; furthermore the duration of the dosing needs to be long enough to induce chronic glutathione depletion.

low but not sufficient to induce hormetic responses, and the duration needs to be long enough to induce chronic GSH depletion. However, such dosing is not generally included in animal experiments to evaluate toxicity of any chemical; conventional designs include only several dose points over a very wide range including a non-exposure control group. Also, chronic or lifetime exposure is not preferred by researchers for the practical reasons of money and time. Therefore, it is not surprising that this harmful zone with very low dose POPs has been little studied by toxicology researchers and is missed in traditional hormetic dose–response relationships (figure 1).

On the other hand, POPs have been reported to show hormetic effects in experimental settings[35 48 49]; certain non-toxic levels of exposure show benefit compared to non-exposure. However, it is difficult to judge whether there is a clear beneficial dose zone in humans. Owing to the ubiquity of background POP mixture exposure, virtually everyone has some exposure; consequently all human studies of POPs lack a no exposure reference group. Epidemiologists can only make relative comparisons of risk of diseases among persons between different exposure ranges of POPs. However, recent epidemiological findings about POPs[5 31 32] demonstrated that there is likely to be some counteracting biological mechanisms which could explain the failure of harmful effects of very low dose POPs to increase with the increasing dose of POPs. Therefore, the aspect of research findings reflecting hormesis in human studies of POPs is that harm observed with a very low dose of POPs does not increase or sometimes decreases as dose increases.[5 31 32] Also, in human studies in the general population, it is almost impossible to observe harmful effects which occur in the toxicity range of POPs. All these differences in terms of exposure ranges and durations lead to apparently different shapes of dose–response relationships between experimental animal and human studies.

HOW CAN THE HORMESIS CONCEPT SUGGEST HOW TO COUNTERACT GLUTATHIONE DEPLETION AND MITOCHONDRIAL DYSFUNCTION OF VERY LOW DOSE POP MIXTURES?

Although the term hormesis arose in toxicology, the hormesis concept has recently received attention in aging research.[46] In a broader sense, hormesis is represented by mild stress-induced stimulation of protective mechanisms in cells and organisms resulting in biologically beneficial effects.[50] The core concept of hormesis is that beneficial adaptations occur in response to an increase in ROS and electrophiles.[51] Mechanistically, redox-sensing transcription factor nuclear factor erythroid 2-related factor (Nrf2) plays a pivotal role in the expression of a range of hormesis-related cytoprotective genes.[52] While there is no question that high levels of ROS cause cellular damage and increase the risk of many diseases, certain levels of ROS function as signalling molecules that promote health by preventing or delaying a number of chronic diseases, and ultimately extend life span.[51] In fact, the prevention of these ROS signals is discussed as a possible mechanism on why antioxidant supplements failed to demonstrate any potential improvements to health in clinical trials.[53]

Stressors inducing hormetic effects include a variety of external and internal stimuli which can increase ROS.[54 55] At the hormetic dose of these stressors, an increase in ROS may stimulate up-regulation of antioxidant, detoxification and survival mechanisms on the cellular and organism levels, thus providing a robust defence against larger and potentially more dangerous oxidative or toxicological stressors.[52] Importantly, molecular pathways explaining hormetic effects include induction of GSH synthesis and promotion of mitochondrial biogenesis.

We suggested above that chronic exposure to very low dose of POPs can induce GSH depletion and mitochondrial dysfunctions during the process of normal metabolism of POPs. Despite increasing ROS in relation to GSH depletion and mitochondrial dysfunctions, ROS due to very low dose POP levels may be insufficient to stimulate a stress-induced protective response. However, at increasing POPs dose, the amount of ROS can increase through several pathways including phase I metabolism and doses can reach a hormetic dose. Then, the depletion of GSH and mitochondrial dysfunction can be reversed through increased GSH synthesis and mitochondrial biogenesis. With further increases in POPs dose, toxicity becomes likely.

As noted above, very low dose TCDD depleted GSH contents, but increased GSH contents in various organs with increasing doses of TCDD in a hormetic response.[20] Also, in

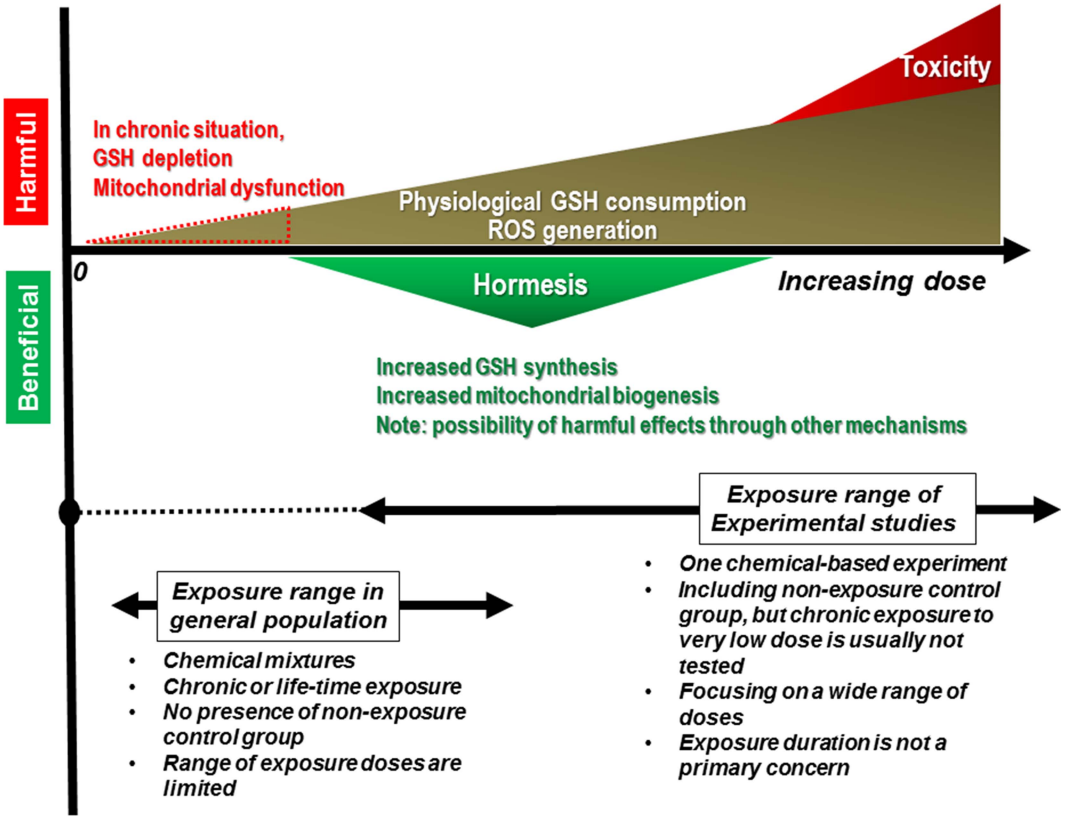

Figure 2 With a range of persistent organic pollutant (POP) concentrations among the general population, there are two zones; increased risk of disease and decreased risk of disease. The increased risk of disease is observed with chronic exposure to very low dose POPs, possibly through glutathione (GSH) depletion and mitochondrial dysfunction. As doses increase, hormetic effects, mild stress-induced stimulation of cellular protective mechanisms, are induced by reactive oxygen/nitrogen (ROS) signals. Increased GSH synthesis and increased mitochondrial biogenesis are well-known biological effects of hormesis. Therefore, the increased disease risk observed with a very low dose of POPs could be weakened by increasing POPs dose as POPs generate ROS sufficient to induce hormetic effects. Importantly, even in the hormesis zone, harmful biological outcomes are possible through other mechanisms including endocrine disruption. On the other hand, the shape of non-monotonic dose–response relation can be different depending on a range of exposure dose. In the general population, there would be few persons with exposure dose in the toxicity range of POPs. Thus, the possible harmful zone associated with a very low POPs dose and the hormetic zone are mainly observed in human studies. However, unlike the exposure pattern in the general population, conventional animal experimental studies employ a wide range of doses (often above background exposure levels), individual chemicals (rather than chemical mixtures) and acute or subacute exposure. Therefore, conventional experimental studies may mainly observe the hormetic zone and the toxicity zone, but miss the possible harmful zone associated with chronic exposure to a very low POPs dose.

vitro studies demonstrated that the treatment of PCB metabolites in HepG2 cells increased ROS, but also activated Nrf2 pathway, leading to the expression of many cellular defensive enzymes like NAD(P)H: quinone oxidoreductase 1 and haem oxygenase 1.[56 57] Thus, the findings suggest hormetic effects through the generation of ROS within certain ranges of PCBs. Figure 2 summarises how different doses of POPs can have different effects in humans, as well as differences between laboratory experimental conditions and the situation of people in the real world. However, these kinds of responses are not specific to any one chemical. A variety of chemicals including phytochemicals, pharmaceutical drugs, and man-made chemicals like POPs can induce the same stress response leading to the activation of Nrf2 pathway.[10]

THREE CATEGORIES OF HORMESIS-INDUCING STRESSORS

Although certain levels of POPs may decrease the risk of chronic diseases through hormesis, it is not advisable to increase background POPs exposure to hormetic levels; the reasons are discussed below. On the other hand, there are other diverse stressors which can induce similar biological effects with a wide human application, and which might help to attenuate GSH depletion and mitochondrial dysfunction by very low dose POP mixtures. Laboratory researchers often classify stressors depending on detailed molecular mechanisms involved in hormetic effects, but it may be more meaningful for the public to classify them based on public health utility. What kinds of external stressors would be acceptable in humans? Here we classify them into three categories; (1) disadvantageous stressors which should not be used, (2) neutral stressors which are appropriate for use and (3) advantageous stressors which should be actively encouraged and used (figure 3).

Typical examples of disadvantageous stressors are toxic chemicals and radiation. A wide range of chemicals can show hormetic effects through ROS generation and Nrf2 activation.[10] Low dose radiation is another stressor which shows beneficial effects with the similar mechanism.[58] However, the possibility of benefits of low dose chemicals or radiation is vigorously debated and deliberate public health applications of these stressors would not be recommended.[38] First, we do not know whether hormetic effects of an individual chemical as observed in an experimental setting can be generalised to chronic or life-time exposure to chemical mixtures.[38] In addition, there are likely to be some highly susceptible individuals to harmful

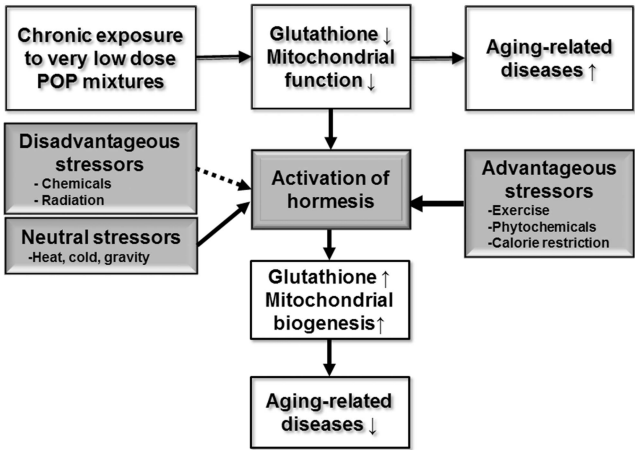

Figure 3 Chronic exposure to very low dose persistent organic pollutant (POP) mixtures can increase the risk of aging-related diseases by the depletion of glutathione and mitochondrial dysfunction. However, hormesis can reverse this pathway. Diverse stressors which can induce hormetic effects in experimental settings can be divided into three categories, depending on their possibility of application to pubic: (1) disadvantageous stressors: chemicals like POPs and radiation, but these cannot be applicable to humans because of issues like chemical mixtures, endocrine disruption and susceptible populations, (2) neutral stressors: cold, heat and gravity which are appropriate for controlled human use, and (3) advantageous stressors: moderate exercise, phytochemicals in plant foods, and calorie restriction are active stressors that have wide human applicability. As background POPs exposure is continuous, the activation of hormesis through advantageous stressors should be integrated into daily life in humans in an attempt to counteract glutathione depletion and mitochondrial dysfunction caused by chronic exposure to very low dose POP mixtures.

effects of chemicals, possibly narrowing the range of their hormetic zones.[38] Furthermore, harmful biological outcomes through other molecular mechanisms including endocrine disruption are possible within the hormetic dose range.[33] Finally, transient ROS signal is the most efficient form to induce hormetic effects.[59 60] Even when the amount of ROS is in the hormetic zone, persistent ROS at this level may badly behave in the long term. Unlike advantageous stressors which can transiently increase ROS, persistent chemicals like POPs and radiation are disadvantageous.

Physical stressors like cold, heat, or gravity may be neutral stressors.[61] Depending on season, residency, occupation or hobby, humans can be exposed to these stressors. Extreme environments in temperature or gravity are of course dangerous or sometimes fatal, but moderate and intermittent exposure may be beneficial to health.

Advantageous stressors are what we can actively use. Typical examples are moderate exercise, phytochemicals in plant foods or calorie restriction.[62–64] Even without any consideration of the hormesis concept, these are much studied behaviours which have been observed to be associated with improved public health. Thus, these stressors can be recommended to the public for the additional reason that they are likely to mitigate harmful effects of chronic exposure to very low dose POPs through hormesis. Compared to chemicals or irradiation, these stressors may be safely used by the public without a big concern for toxicity, even though in extreme cases these stressors can be harmful as well. In support of this concept, a recent study reported that serum carotenoid concentrations related to diet high in phytochemicals was associated with reduced risk of dioxin-like PCB-associated type 2 diabetes.[65] This result was interpreted by the authors as the result of multiple actions of carotenoid itself including antioxidant activity[65]; however, this study can be seen as an example linking hormetic effects of phytochemcials to counteracting harmful effects of POPs as carotenoid can activate hormesis through the activation of Nrf2 system.[66]

CONCLUSION

Recent human findings on very low dose POPs suggest chronic disease risk from living in chemical-contaminated modern societies, and lead to the question of how we can protect ourselves against this harm. Conventional approaches to harmful chemicals like regulation or avoidance of exposure sources are necessary and important, but have only had a limited effect, given that POPs continue to persist in food chains and our adipose tissue despite many POPs being banned decades ago.

However, gradual GSH depletion and mitochondrial dysfunction, important biological mechanisms in the pathogenesis of many chronic diseases, due to chronic exposure to very low dose POP mixtures can be reversible by hormetic effects of various stressors. Even though POPs themselves appear to show hormetic effects, it is dangerous for the public to increase POPs exposure with the aim of inducing hormesis because of issues like chemical mixtures, endocrine disruption and susceptible populations. Also, the persistent nature of POPs can make hormetic effects less effective in human as hormesis may be the most active with transient stressors. Similarly, other harmful chemicals and radiation cannot be recommended for the public.

However, this form of hormesis is shared between POPs and other stressors which are safe and well-accepted by the public. They include moderate exercise, phytochemicals in plant foods and calorie restriction. Hormesis is a biological reality and very likely is one mechanism underlying the benefits of a healthy lifestyle. Many of the commonly issued public health recommendations involving lifestyle modifications make use of hormetic principles, whether knowingly or unknowingly. As exposure to very low dose POP mixtures happens continuously in our daily lives and they persist in our bodies and our food chain, the activation of hormesis by advantageous stressors should be integrated as a part of daily life. While there is nothing new about a call to eat a plant-based diet in small portions, accompanied by exercise, the recognition that such public health action might ameliorate some adverse effects of POP mixtures is worthy of note.

Contributors DHL conceived the hypothesis and wrote the paper. DRJ edited the paper and contributed the interpretation.

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