The Environment and Endocrine Disrupting Substances:

At what level are they harmless?

Hormones play critical roles in the development and management of the reproductive system - including sex characteristics; the coordination, development and function of tissues; the nervous system and brain (behaviour and intelligence); in mediating the immune system and in development of hormonally relevant cancers such as breast, testicular and prostate cancer. Hormones act at parts per million, billion and trillion (PPB). Hormones work in concert - in a highly integrated manner.

Endocrine (hormone) disrupting chemicals (EDCs) can mimic or perturb hormones to harm health. Daily exposures from food, food packaging, personal care products, detergents and house-hold chemicals, via airborne pollution and drinking water can cause disruption. Neonatal, prenatal end childhood exposures can cause harm that may not be observed until years later. EDCs may adversely harm multiple pathways at the same time. Hormones act similarly in all vertebrates are reasonably well understood. It is almost impossible to unpick when EDC action commences.

Because of such complexity, it is unlikely precise end-points for endocrine disrupting chemicals can be developed in the next ten years, if scientifically determined principles of endocrinology are taken into account. There is no safe end-point. Scientists understand that there can be no safe level of exposure to EDCs, carcinogens, nor mutagens.

'*We often cannot predict the tipping points or thresholds of irreversible damage*' (Iorns, 2018).

A Planetary Chemical Burden

Environmental chemicals production has surged over the last 20 years – global chemical production (including pharmaceuticals) roughly doubled between 2000 and 2017. There are 40,000-60,000 industrial chemicals in commerce globally. 6,000 of these chemicals constituting 99% of the total volume. A European report considered 62% of the total volume consumed to be hazardous to health (UNEP, 2019, p. 3).

Chemical production is considered to be the world's second largest manufacturing industry. In 2017 the industry was worth more than US$5 trillion. This is expected to double by 2030. (UNEP, 2019)

Scientists have known EDCs can damage human health and contribute to global disease burdens for decades. Effects from exposure to EDCs may be short term or long term, and they may occur across generations (Colborn, Myers, & Dumanoski, 1997). In a 2019 paper commissioned by a committee of the European Parliament, endocrinologist Professor Barbara Demeneix and environmental epidemiologist Rémy Slama noted that the damage incurred by EDCs 'include obesity and metabolic disorders, reproductive disorders, reproductive cancers, thyroid disorders, neurodevelopmental disease and IQ loss'. They also drew attention to the annual costs from impairment and disease in the European Union, estimated to be EU163 billion annually (Demeneix & Slama, 2019).

Scientists consider reducing exposures of chemicals would result in a decrease of 2.7% of global deaths from preventable disease - and that this is an underestimate. The Lancet Commission on Chemical Pollution and Health identified chemical pollution as a significant 'and almost certainly underestimated' contributor to the global burden of disease (Landrigan PJ & et al, 2017).

Conventional toxicological research does not consider that exposures at exceedingly miniscule hormone levels may be more harmful than effects at a higher dose. (Colborn, Myers, & Dumanoski, 1997) Hormone receptors are extremely sensitive to extremely low doses (E.g. PPT) and the response is highly complex - dependent on hormone concentration, receptor affinity, receptor abundance and co-regulatory proteins, for example. Non-monotonic (non-linear) dose responses are not rare – they often occur, and individual response can be dependent on life stage.

Scientists agree EDC is a serious concern for health

A paper submitted to the European Parliament noted that scientific consensus exists for:

1. the definition of endocrine disruptors;
2. the presence of suspected or recognized EDs in the environment and in humans in Europe;
3. EDCs pose a serious concern for the health of current and future generations and the environment;
4. the limitations of current regulatory approaches to identify so-called safe thresholds
5. the greater risk from combined chemical exposures. (Demeneix & Slama, 2019, pp. 11-12)

The paper stressed that the human foetus is particularly vulnerable during 'foetal development due to the immaturity of homeostatic mechanisms and absence of endocrine feed-back loops or immaturity of toxicokinetic defence/detoxification mechanisms as compared to adult life stages' (Demeneix & Slama, 2019, p. 6). Many adverse EDC exposures during development have been found to be irreversible.

Scientists consider more chemicals interfere with the thyroid hormone than any other system. All vertebrates depend on the same chemical structure of thyroid hormone. The thyroid hormone plays a critical role in brain development and myelination particularly in the last months of pregnancy and first two years of human life. Thyroid signalling is a bridge between the environment and gene function. (Demeneix & Slama, 2019)

Problematically, toxicological risk assessment for chemicals relies on 'endpoints' on which to base an authorisation. However, EDCs may impact multiple pathways and risk variables may differ for a given EDC for one chemical. For example the threshold for action on brain development may be markedly different from the threshold for fertility or risk of hormone dependent prostate or breast cancers (Gore, et al., 2015).

There is plausible evidence that ***no safe thresholds*** (below which no effect will occur) can be identified for endocrine disrupting chemicals and compounds. Regulatory tests are not sufficiently sensitive and 'may identify experimental thresholds for EDs, but these are expected to represent the limit of sensitivity of the test rather than constitute a biological threshold valid in human populations in their diversity' (Demeneix & Slama, 2019, p. 78). The marker between *no* effect and *some* effect is extremely difficult to measure, and this is complicated by different life-stage biological vulnerabilities. Some EDCs can bind to multiple hormone receptors. Thus 'potency' for an EDC will always be an imprecise concept. Scientifically, it is almost impossible to detect the level where EDC exposures are benign.

Chemical regulation for environmental chemicals under New Zealand legislation are based on no observed effect level (NOEL), requiring the identification of thresholds (PCO, 2019). Risk assessment can either (a) assume a biological threshold exists, derive a dose level from an experimental NOEL and incorporate uncertainty factors to derive an acceptable exposure level that critics will accept. Alternatively, (b) *recognise the inherent uncertainty of biological thresholds and that there may be many modes of action that may lead to harm.* The latter approach – the 'non-threshold approach' results in precautionary regulatory risk management measures, by ceasing authorisation of a product or limiting exposure so that the public may not be exposed. *This precautionary approach recognises the limit of current assays to detect harm.* It is important, for example, that consideration takes into account the fact that low concentrations of EDCs can add to hormone concentration at the low end of the dose-response curve. This is where substantial risk may exist, as the effect can 'produce substantially effect greater differences in effect than similar changes in hormone concentration at the high end of the dose-response curve' (Gore, et al., 2015, p. E11).

The 'heterogeneous regulation of EDs in different sectors is hard to justify scientifically' (Demeneix & Slama, 2019, p. 78). Biological thresholds depend on many parameters and vulnerability will vary, depending on age, specific tissue sensitivities, existing diseases or the integrity of detoxification reparation mechanisms. In contrast, regulatory thresholds are based on *limited experimental thresholds* – the dose below no effects are observed using specific tests with safety (or uncertainty) factors incorporated to obtain the threshold (Demeneix & Slama, 2019, pp. 50-51).

Modern regulatory testing has been criticised for relying on industry to select and supply the data, and for using active ingredient toxicological data to establish endpoints rather than requiring that risk assessment be based on the

toxicity of the (more toxic) retail formulation. There are other limitations, for example OECD guidelines may not be sufficiently sensitive, as they do not allow for the subtle mechanisms that can signal toxicity (such as changes in organ weight), different responses from route of exposure, issues of non-monotonic dose response, and the failure to consider the effect of combined exposures, and the delicate responses at PPT and PPB.

Current regulatory frameworks are not sufficiently protective to protect human and environmental health from EDC disruption. For example, the New Zealand Environmental Protection Agency's approach to pesticide regulation is outdated and its capacity to exercise precaution is weak (Iorns, 2018). Endocrine disruption is not considered as an equivalent health risk as risk from carcinogenic, mutagenic or reproductive substances. If submissions for assessment do not include endocrine disruption, this need not restrict the approval process. New Zealand has few scientists working in this field with specialisation who might advocate for change. In Europe, pesticides regulation is the most advanced regulatory sector of EDCs (ECHA, EFSA, et al.,, 2018). If substances are identified as EDCs or presumed EDCs, European regulations will not authorise (or re-authorise) the substance. However, the regulations are currently weak as the tests listed in the requisite dossiers are not compulsory.

There is sufficient evidence that a policy approach that insists that precise (and scientifically implausible) 'safe thresholds' are derived, have the effect of delaying an appropriate response. The current state of science knowledge demonstrates this is not sufficiently protect environmental and human health under principles of administrative law.

Medicine accepts non-linear / non-monotonic dose response

In medicine, it is accepted that endocrine disrupting chemicals (as drugs or environmental exposures from toxic substances) can damage or disrupt hormone function. Rather than use the term 'non-linear dose response' or 'non-monotonic dose response curve' (NMDRC), medical practitioners may refer to the effect as a 'flare'. Flares can be due to a dose of a drug or chemical interfering with hormone function at PPB or PPT. This effect is reproducible.

Vandenberg and co-authors in 2013 in a paper discussing NMDRC, highlighted clinical cases where drug reactions were more harmful at lower hormonally relevant doses than at higher doses. Tamoxifen produces NMDRCs at low concentrations in the blood, Tamoxifen stimulates tumour growth, and at high concentrations tumour growth is inhibited. The drug Lupron has been found to induce ovulation, while at high doses, the ovarian response is supressed (Vandenberg, et al., 2013). The authors noted that *if* NMDRCs are a rare event, then current regulatory practices may not be confounded by their presence, whereas if they are common, they should be an important component of regulation. NMDRCs may occur in 12-24% of all dose response studies. (Vandenberg, et al., 2013)

Environmental Pollution

Manmade chemicals contribute to ecological disasters and damage health, at an acutely toxic level, but also at low levels – at parts per trillion (PPT). Chemicals contribute to aquatic 'dead zones', while lower levels of chemicals can threaten the ecological integrity of water bodies and distort the balance of flora and fauna, rendering environments inhabitable for native species. Insect population decline has been linked to constant, chronic exposure to low levels of pesticide mixtures (UNEP, 2019).

Drinking Water and Freshwater: Public officials acting under the New Zealand Resource Management Act have an obligation in law to safeguard the life-supporting water and ecosystems; and avoid adverse effects of activities on the environment. However, monitoring to understand cumulative low dose effects is not required through national policy frameworks. This makes it impossible to understand diffuse chemical signatures and shift towards greater regulation. Public investment in EDC science, monitoring and regulation of EDC chemicals in New Zealand is poor.

The national focus on environmental pollution has been arbitrarily restricted to 'nutrient' and 'sediment' issues, with public attention diverted away from synthetic chemical pollution originating from agriculture, industry and urban waste sources. There are few scientists with basic science expertise in this space with a remit to engage in public debate. PSGR and the Soil & Health Association released a white paper in 2019 discussing this problem.

Recommendations to protect human and environmental health:

Doing nothing – not researching human health effects, not monitoring, nor establishing controls where there is evidence that endocrine disrupting substances and mixtures are present, ensures that only the polluting industries are protected. There are policies and procedures that ensure nations can move forward responsibly and iteratively:

- Confirm EDCs constitute a distinct class of health hazard, equivalent to carcinogens & mutagens
- Adopt legal protections requiring neonatal and paediatric exposure to EDCs are avoided
- Require that substances identified as known or presumed EDs should not be authorized ("no exposure" logic) in products with general population exposure (Demeneix & Slama, 2019, p. 98).
- Institute data collection by Statistics New Zealand of synthetic organic compounds and active ingredients imported and produced in New Zealand. This will ensure top down measuring to assess risk, that may then be bottom up monitored for environmental and human health exposures.
- Data collection can identify high volume chemicals that currently evade regulatory controls. e.g. glyphosate.
- Once degraded water regions are detected, commence national screening for diffuse levels of synthetic chemicals (agrichemicals, plastics, industrial chemicals, pharmaceuticals, heavy metals, and sewerage).
- Precaution must operate at a meta-level. Caution must not be one factor that a decision-maker must take into account. *A precautionary approach is more than just part of risk assessment.* Precaution is meant to guard against the unknowns and unanticipated consequences' (Iorns, 2018, p. 47).
- Fund predictive analytics (data modelling, machine learning) to predict mixture stress from endocrine disruptors, carcinogens and mutagens to biological systems (human and aquatic) (Soil & Health Association and PSGR, 2019).
- Monitor oestrogenic, androgenic, thyroid, steroid loads in drinking water.
- Institute public funding for environmental and public health expert taskforces (in endocrinology and toxicology) separate from chemical industry influence to:
    - Research endocrine disruptors in the New Zealand environment and in human tissues;
    - Research pathways EDC can harm health from a basic science 'public interest' perspective;
    - Share knowledge & work with international public health agencies to develop guidance documents;
    - Develop a public health mandate to accelerate test development and validation protocols.
- Recognise that in the interests of public health, export markets and environmental integrity, supporting, liaising with and harmonising with best practice jurisdictions (e.g. European Commission) may be the most effective, up to date and transparent method for controlling EDCs in the New Zealand environment.

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