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Endocrine disruption technique a better tool of green chemistry for developing new chemicals.

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Abstract

Green chemistry's main purpose is to prevent danger in the development of new chemicals. This goal is best accomplished by gathering knowledge regarding a chemical's potential harmful effects as early as possible in the design process. Endocrine disruption is a form of hazard that has received insufficient attention from both industry and regulatory scientists to yet. We suggest an endocrine disruption testing technique for use by chemists in the creation of novel substances to help them avoid this hazard. The Tiered Protocol for Endocrine Disruption (TiPED) was developed with the help of a scientific advisory council made up of notable figures from the fields of green chemistry and environmental health. A testing technique must be able to quantify potential hormone-like or hormone-inhibiting effects of chemicals, as well as the various possible interactions and signalling sequellae such compounds may have with cell-based receptors, to be effective in detecting endocrine disruption. As a result, we've created this approach to probe the endocrine system comprehensively. Because scientific awareness of these phenomena is continually improving, the suggested approach will not identify all probable pathways of endocrine disruption. To keep the technique up to date, we've devised a strategy for adding additional assays as research progresses. To The concepts that should drive the science of testing novel compounds for endocrine disruption, as well as criteria for evaluating particular tests for application and laboratories for reliability, are presented in this study. We ran six endocrine disrupting chemicals (EDCs) that operate via diverse endocrinological processes through the methodology utilising available literature as a "proof-of-principle" test. One or more layers designated each as endocrine active. This voluntary testing technique, we hope, will be a dynamic instrument for facilitating efficient and early detection of potentially harmful substances, hence lowering public health concerns.

Key Word : Endocrine ,green chemistry,EDC , TIEPD .

Introduction

Most attempts to reduce chemical risk to human health have concentrated on minimizing the likelihood and amount of exposures, as Anastas and Warner point out. That strategy works until it doesn't. Unfortunately, failure is nearly unavoidable due to mishaps and behaviours that are not part of the 'planned usage of a product.' Accidents like the inadvertent release of methyl isocyanine gas in Bhopal, BP's Deepwater Horizon oil leak, children recycling electronic debris in China and India, and home dust carrying flame retardants in California are just a few examples of unintended exposures.

Green chemistry, on the other hand, takes a different approach. One of its main objectives is to create chemicals that are safe for human health and the environment. Chemists must be able to identify the possible risks of the compounds they manufacture in order to attain this aim efficiently. We use the word 'hazard' purposefully since it is one of the two deciding aspects of risk in green chemistry. Risk is widely acknowledged to be a consequence of inherent danger and exposure. Green chemistry approaches risk by attempting to eliminate the source of the danger rather than limiting exposure . This evaluation should take place as early as possible in the design phase so that decisions may be made about whether or not to pursue future development. If a hazard is discovered, the chemist has two options: stop developing the chemical or change the molecular structure to design around it. In an ideal world, new compounds' potential toxicity might be predicted with certainty based on their structure and physical features. However, well-known flaws in these methodologies (such as the 'Structure Activity Relationship Paradox' outlined below) make this approach not only insufficient, but possibly deceptive. Such a high risk of false positives and negatives is unacceptable in our undertaking. As a result, actual biological experiments are required.

Because chemists aren't often educated in toxicology or other related subjects, collaborating with environmental health experts and green chemists is required to find the tools to attain this aim. This partnership, if done consistently and altered to reflect new scientific discoveries, might lead to a new generation of compounds that are fundamentally safer.

In this paper, we look at how chemists might use ideas and tests from the physical sciences to help them solve problems.

To find possible endocrine disruptors, scientists are looking at environmental health sciences. Specifically, TiPED is a five-tiered testing procedure that we suggest. We'll start with computation. techniques as the quickest and most cost-effective tests The following layers entail

Increasingly sophisticated tests are being used to evaluate whether a substance has the potential to disturb the endocrine system. Characteristics of a chemical that is currently being developed. Some of the tests are predicated on the results of others. Some are meant to capture disruptions for which there are no known mechanisms of action; others are designed to catch disruptions for which there are no known mechanisms of action. Mechanisms or receptors have yet to be discovered. The broad framework of the project is shown. Each tier has a protocol with examples of assays that might be utilized.

For a scientist building a novel chemical, we give the tiers in a logical order: from the simplest (and least expensive) to the most complicated (and often more expensive). However, we acknowledge that various users will have different requirements. A user can begin at any point in the system, not just Tier 1. An academic research chemist who is creating a molecule from scratch will face different challenges and questions than an industrial chemist who already has a molecule; the former is more likely to follow the process in a linear fashion. Later-tier tests might be used by the latter to gain a rapid read on the likelihood of possible difficulties. Some users may prefer a simple "damage/no likely harm" response, discarding failed compounds.

What is endocrine disruption, and how does it happen?

Chemical signals called hormones are used by the endocrine system to control growth and reproduction, regulate bodily function and metabolism, and impact behaviour and immunity . Endocrine disruption occurs when an agent disrupts hormone signaling or the response to hormone signalling, and thereby affects some element of the organism that is controlled by hormones. An endocrine-disrupting chemical (EDC) is an exogenous molecule, or mixture of chemicals, that can interfere with any element of hormone activity, according to the Endocrine Society, the world's preeminent scientific society of clinical and research endocrinologists .

Different processes can induce endocrine dysregulation. Hormones bind to protein receptors in the cell membrane, cytoplasm, and nucleus to act.

Binding begins gene activity or physiological processes that are part of and crucial to proper organismal function (depending on the receptor, its location, hormone concentration, and the developmental state of the cell/tissue/organism). Interfering with the signaling pathway is how EDCs function. They are not all lipophilic; many, but not all, are structurally comparable to hormones.

The EDC affects hormone synthesis (increasing or decreasing the amount of natural hormone available for signalling); the EDC affects hormone metabolism or hormone transport and storage within bodily tissue (again, increasing or decreasing hormone amount); and/or the EDC affects the levels of mature hormone receptors.

Me The receptor binding that occurs as a result of endocrine disturbance is dependent on the molecular conformation of the hormone and its receptors. Molecular structure is a good, but not perfect, predictor of whether binding will occur; scientists may utilise structural information to identify possible hazards as well as to predict whether binding will occur. (Explained below), as well as to guide the altering of a chemical's structure in order to prevent problems. hazard.

MA One of the most important aspects of hormone activity is that it occurs at extremely low quantities. Typical physiological levels of the physiologically active version of an oestrogen, for example, are extremely low, ranging from 10-900 pg/ml 8 (high parts per quadrillion to low parts per trillion). Because of the huge number of signalling molecules present at any one moment, this is achievable due to the specificity of hormone binding to its receptor. It is also biologically required. Because of their high specificity and sensitivity, a large number of signalling molecules may coexist in the bloodstream without interfering with one another's signalling. The specialization probably arose to decrease or prevent disruption by external substances with which organisms have adapted to deal.

M Over 80,000 novel compounds have been created and utilised in ways that have resulted in widespread human exposure in the last century. A subset of these compounds is poisonous, and another group is harmful owing to endocrine disruption. disruption. A tiny number of these compounds were produced specifically to change the environment. numerous pesticides (for example, the estrogenic chemical diethylstilbestrol) and hormone signalling (species of interest). Other substances have molecular structures that accidentally exhibit a resemblance to each other.

sufficient similarity to hormones to allow binding, with different degrees of success degrees of affinity for hormone receptors or molecular interactions with them additional substances that play a role in hormonal action EDCs are frequently far less powerful than other types of drugs.

Endocrine Disturbance Testing

Because of the complexities of endocrine disruption biology, no one assay or technique can be utilised to detect compounds that have EDC properties. Instead, a mix of methodologies, including computational methods as well as in vitro and in vivo testing, is required. A correctly constructed battery of tests can greatly minimise the risk that a newly created chemical would subsequently be discovered to be an EDC, compared to present practice. Many forms of EDC activity may be tested in vitro. Endocrine disruption, on the other hand, occurs when one or more hormones in a complete organism are disrupted. The intricacy that this entails is not accounted for in today's in vitro and computer models. As a result, in vivo experiments will also be required. Two more endocrine system features must be considered while developing a strategy.

detect possible EDCs To begin with, EDCs, like endogenous hormones, can have nonmonotonic dose-response curves . This means that effects seen at low doses can be replicated at higher doses.

Levels can be utterly unexpected, and can even be the polar opposite of reported effects.

At a really high level The non-monotonicity of the endocrine system is due to a number of processes. systems. Thus it is critical to assess chemicals over a wide concentration range in vitro

To see if they have EDC properties, they must be tested in vivo across a large dosage range.

Second, the consequences of EDC exposure differ depending on the period of life at which it occurs. As a result, the effects of exposure at distinct stages of development (foetal, childhood, and adolescent, including puberty) might differ significantly from one another and from adulthood exposures. While adult exposure to EDCs can probably have a role in negative health consequences, crucial developmental stages are likely to be more vulnerable to endocrine disruption.

During developmental transitions, adverse effects are likely to occur at chemical concentrations that are significantly below those that would be deemed dangerous in adults . These sensitive life phases, such as foetal, childhood, and pubertal development, are especially concerning since the individual is changing physiologically and morphologically during these times. Massive changes in the endocrine environment accompany the development of the new phenotypic (or body plan) throughout these transitional times. Multiple reasons contribute to this increased sensitivity throughout developmental changes. Most importantly, hormones' organisational functions (organ creation, brain structure, etc.) are irreversible, but their activational functions (reproduction regulation, immune system modulation, etc.) are reversible in adulthood. Second, in the foetus or infant, protective systems such as DNA repair processes, a functioning immune system, detoxifying enzymes, liver metabolism, excretion, and the blood/brain barrier are not completely functional. Third, the metabolic rate of a developing organism is higher than that of an adult or elderly organism, which may result in greater or decreased toxicity in specific instances.

TiPED Tier 1: Computation-based assessments

Assessing the physical and chemical characteristics of a molecule, such as density, boiling point, vapour pressure, refractive index, viscosity, surface tension, polarizability, partition coefficients, logP, and so on, would be a sensible starting point for a chemist building a chemical from scratch. Tier 1 includes a variety of computational methodologies that anticipate EDC characteristics of compounds using statistical, computer, and mathematical models. In comparison to higher tiers, early-stage detection of potential for endocrine disruption employing in silico approaches provides the very desirable benefits of speed, reduced cost, efficiency, avoidance of animal usage, and sustainable resource management.

There are four unique, complementary approaches to computational-based evaluations currently available:

- Chemical reactivity: These approaches are based on the presence of a toxicophore, a specific chemical group within a larger molecule with identified toxic properties, as defined by Williams (2002), such as the 1,3-benzodioxole group containing molecules in kava extract, or azo-fragment (R-N=N-R') in some dyes.
- Physico-chemical properties: Statistical toxicity forecasts based on physico-chemical factors like lipid solubility and octanol-water ratio. The partition coefficient, or logP, is a hydrophobicity metric that corresponds with common contacts and specific elimination/activation routes.
- Q/SAR: methods based on the notion that compounds with comparable properties are related. Chemical structures will have biological actions that are comparable.
- Modeling of biological activity: this method use a flexible 3D model of the novel molecule to forecast whether it would fit into the binding pocket of a specific biomacromolecular target linked to an endocrine disruption pathway, such as a nuclear hormone receptor.

Quantitative/Structure Activity Analysis (Q/SAR)

In the mid-1960s, a series of studies lay the groundwork for quantitative research.

Quantifying connections between a set of activities (Q/SAR) helps to organise activity linkages. The biological activity of a substance as well as its physicochemical characteristics . The Q/SAR (Question/Answer Ratio technique makes use of statistical tools to create biological activity prediction models based on a variety of descriptors specific to the molecular structure/properties of a chemical (For example, molecular weight, the quantity of H-bond acceptors/donors, log P, solubility, and so on.) The structure and molecular characteristics of the test chemical are then compared to those of a control chemical.

An experimental data set's structure and properties (a training set of well characterized molecules where biological activities are well established). The objective is to with the goal of determining structural similarity to other compounds with established biological action. presumption that the untested molecule has the same biological action as the tested molecule developing a meaningful Q/SAR prediction model for toxicity is difficult and depends on a number of criteria, including the quality and availability of biological data, the statistical methods used, and the descriptors used. The biological activity of the chemical and its physico-chemical properties would be included in a viable Q/SAR model .

1) Include a training set with a large enough number of molecules to cover the model's projected range of attributes.
2) The number of compounds in the training set should be at least 5 to 10 times more than the number of non-correlated descriptors used to compute the model. In addition, the descriptors should be biophysically relevant to the expected attribute.
3) The model should be adaptable to new chemicals and include mechanistic knowledge about the desired endpoint.
4) The simplest model should be chosen wherever possible.

When using a Tier 1 technique to forecast EDC potential, a chemist should keep the following limitations of the Q/SAR methodology in mind:

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The "SAR Paradox," which is the fact that

Tier 3: In vitro whole cell activity assessment

We use sensitive cell-based assays in Tier 3 that have been shown to correctly represent in vivo signalling and functional outputs in entire cell systems. Individual substances or combinations of EDCs can be used to trigger an integrated response in cell-based assay techniques. This is an important stage in determining if a chemical may activate signalling pathways that result in functional outcomes like cell division, differentiation, or cell death. Tier 3 in vitro HTS experiments are often more complex, requiring more time, money, and knowledge to perform. The focused sensitivity of these tests, on the other hand, will give critical biological confirmation on whether the molecule of interest has endocrine disruptive action.

In Tier 3, we employ sensitive cell-based assays that have been demonstrated to accurately replicate in vivo signalling and functional outputs in whole cell systems. In cell-based testing approaches, single compounds or mixtures of EDCs can be utilised to generate an integrated response. This is a critical step in identifying whether a chemical may activate signalling pathways that lead to functional consequences such as cell division, differentiation, or death. Tier 3 in vitro HTS investigations are often more complicated, requiring more time, money, and expertise to complete. On the other hand, the concentrated sensitivity of these assays will provide crucial biological evidence of whether the chemical of interest has endocrine disrupting activity.

The capacity to analyse functional outputs arising from receptor binding and pathway activation is the fundamental benefit of Tier 3 testing. As a result, a good Tier 3 test is a strong sign of EDC activity. Some of the Tier 3 tests we suggest are currently in use in Tier 2. This redundancy is required for two reasons: first, it addresses concerns about current HTS systems' quality control and the associated frequency of false positives and negatives. Second, Tier 3 allows chemists to go further into particular biological systems that might lead to chemical changes that would reduce EDC activity.

Overarching Principles

Green chemistry provides the first principle. Green chemists create products that are safe to use . The earlier a danger can be identified in the design process, the more probable it is that downstream issues will be

mitigated, if not completely avoided. The pharmacist and his or her firm may profit financially as a result of this.

The second point compares our technique with standardized approaches employed in regulatory toxicology, based on current scientific understanding. As previously stated, the standardized tests that traditional toxicological techniques rely on are sometimes decades old. The quality and sophistication of assay techniques used in scientific research supported by the National Institutes of Health, particularly the National Institute of Environmental Health Sciences, are seldom reflected in them. The previous methods are insensitive and ineffective in dealing with EDCs. Chemists would produce yet another generation of harmful substances if they ignored current research.

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However, the assays we offer were chosen because they have been effectively utilized in numerous laboratories. They may need specific knowledge and abilities, but they aren't so esoteric that they can only be implemented by a single, or a limited number of laboratories. The principle's second part recognizes the rapid rate of scientific progress in the realm of endocrine disruption. New ways of action will very definitely be uncovered, necessitating the development of new assays. It is critical to include this changing information into the protocol.

Using TiPED with known EDCs: verification of methodology

We found numerous known EDCs (chemicals or classes of compounds) that function through distinct mechanisms and have vastly diverse effects on exposed cells, animals, or people when we initially started developing this tiered method to screening novel chemicals. We identified a set of assays that we thought would be sufficient to detect known endocrine disrupting activities based on these examples. To continue this thought-exercise, we then identified \ spublished studies that determined whether the TiPED assays described above (or \ ssimilar ones) have been used successfully with these six known EDCs . Several computational assays in Tier 1 would clearly identify some of these EDCs. Both Q/SAR and molecular docking assays have been used to test BPA and phthalates, and both indicate that these chemicals bind to nuclear hormone receptors. Perchlorate and atrazine, for example, would very certainly "pass" the first rung. BPA would also be detected as an EDC in Tiers 2, 3, 4, and 5 if tested further using TiPED. This tiered screening methodology would easily identify a chemical like BPA, which has processes that span numerous NRs. Perchlorate and atrazine, on the other hand, may not be classified as EDCs until Tiers 3 or 4. However, the proposed tests appear to be sufficiently robust.

Currently, we plan to make the EDC test procedure available to the public. Its home institution has yet to be selected, however it will most likely be an academic institution or a government agency. TiPED's "home" will be a place, no matter where it is. Below you'll find thorough test procedures as well as a list of internet resources. tools and databases There will also be qualified individuals on hand to answer inquiries. and give basic advice and referrals to laboratories that can undertake particular work on a contract basis assays. A Scientific Committee oversaw the protocol's inception and development.

Experts in chemistry and biology make up the Advisory Committee . Oversight and regular monitoring of the process will be required in the future.

Conclusions

TiPED provides resources to aid in the creation of intrinsically safer products. Chemicals that are likely to disturb the endocrine system are avoided in materials. Making use of the protocol's assays Chemists might opt not to pursue development of a candidate chemical that possesses EDCs early in the design process to detect potential EDCs. characteristics. Alternatively, they might utilise the assays' mechanistic findings to guide them. Redesign of the chemical with the purpose of preserving desirable material properties while reducing costs.

We focused solely on scientific issues in order to provide chemists with a set of guiding principles and tools that will enable them to stop the production of chemicals with EDC potential. The goal of TiPED, a ground-up approach, is to identify hazard early in the design process by using a systematic series of assays that build on each other. We want to stress that our tierred protocol was not created to be a one-size-fits-all solution. A chemist may have excellent cause to start at any stage in the procedure, not only Tier 1, depending on their specific scenario.

A positive test at any stage of the process indicates the presence of a possible endocrine disruptor, giving the scientist the option to alter the chemical in development. Each tier's endocrine disruption screening tests are based on the most current and best science; TiPED is meant to address all known elements of endocrine disruption as a whole.

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