Pharm-Ecology.

Much of the work of this lab is inward-looking, in the sense that we focus on the inner workings of the body, and usually do so at microscopic scale. But there is a big world out there, and sometimes what we think about at tiny scales can have important implications at the scale of a planet.

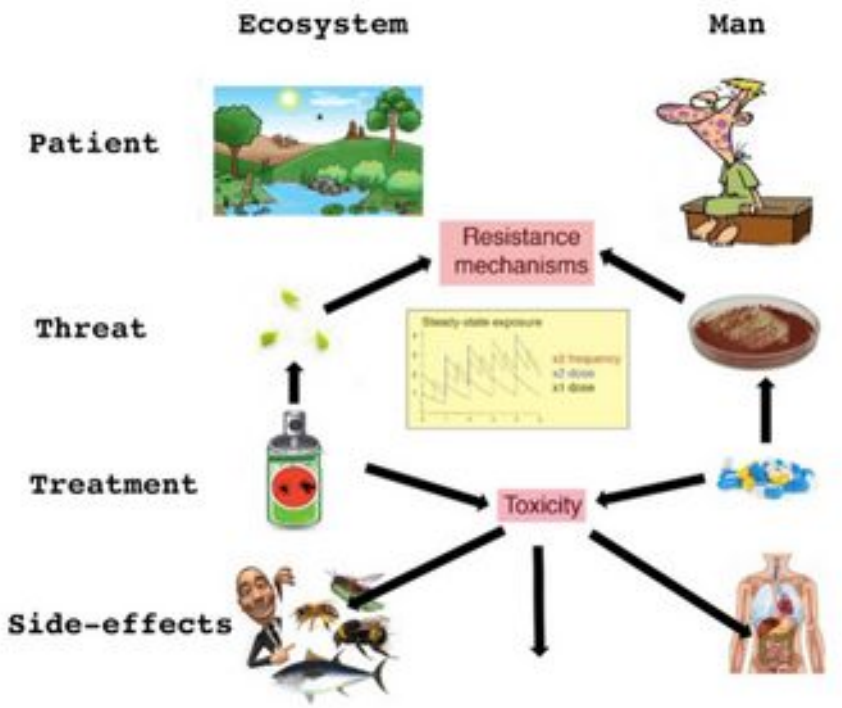
A research paper we – a collaboration of four people in four places – have just had accepted by the British Journal of Pharmacology is an example of this. The basic idea for the paper came from Dr Chris Connolly, an expert in the unfortunate 'side-effects' of agro-chemicals on biodiversity, particularly that of insects. Chris was justifiably frustrated at the way that pesticide use is measured and approved. Typically, pesticide usage is reported as mass of pesticide applied per area of land. According to this measure, UK pesticide use has fallen markedly in the last two decades, which looks like a good news story. Hidden is the fact that, during this time, pesticides have changed and they have become more potent. Absolute mass is not a sensible measure.

Being aware that pharmacologists have more sensible ways of measuring the 'dose' of active molecules in the body than simple mass per kilogram that pays no attention to what the molecule is, Chris decided to link up with pharmacologists for help. He therefore approached members of the 'gang' who run the IUPHAR/BPS GuideToPharmacology database – me as database PI, Michael Spedding as Secretary-General of IUPHAR and Steve Alexander as Chair of IUPHAR's Nomenclature Committee, which also looks after measurement standards – and described the problem.

The result of lots of e-mailing and Zoom meetings has been a proposal for 'environmental pharmacology'. Specifically, that those concerned with pesticide development and environmental protection should transition from mass-per-area as a

metric, to a pharmacologically sound method of measurement that takes into account the potency of a chemical, or mix of chemicals, on the target species and on ‘innocent bystanders’ such as bees.

In human pharmacology, there is a concept of the therapeutic index, which is a measure of the ‘safe gap’ between the minimum concentration of a drug required to accomplish a clinically desirable task, and the maximum concentration that can be tolerated before the drug does unacceptable harm. For



most over-the-counter drugs, this window is wide, meaning that *minor* errors in home-dosing, in terms of how often tablets are taken, for example, are unlikely to do serious harm (though still be careful!). For some prescribed drugs, such as warfarin, the window is so narrow that regular blood checks are needed to ensure that the dose is not exceeded. It is fairly easy to extend this principle to create an ‘environmental therapeutic index’; the window between the minimum concentration of a pesticide requires to control the pest, and the maximum that can be tolerated by bystander species that need to be protected. If this were used as a measure for approval of pesticides, and position in this window used as a metric, it would be much easier to ensure that biodiversity is protected.

Of course, there are complications. One is that pest species evolve resistance, and the minimum concentration needed to control them may therefore rise with time, narrowing the safe window. Another is the complicated relationship between how much a farmer should apply to a field, and the resulting concentration. This depends on the life of the pesticide and how it is finally decomposed. Human pharmacologists are used to this too, in the whole field of pharmacokinetics, and routinely consider mechanisms of ADME (absorption, distribution, metabolism and elimination) in converting target concentrations in the body to dosing recommendations given to doctors. A parallel approach to agrichemical use would be beneficial.

A final complication is how maximum tolerated concentration/ exposure is measured. Instant lethality is too blunt an instrument; some agrichemicals, such as neonicotinoids, have long-term behavioural effects on bee colonies that are too subtle to show up in a simple test about whether an individual bee survives exposure. There is also the question of whether past exposures, including in development, create irreversible harm (an ecological parallel to thalidomide, perhaps). But these complications do not rule out the approach – they only mean that measurement of harm needs to be done intelligently, by following the at-risk species over a whole life-cycle (meaning the life cycle of a whole colony, in the case of social insects).

For a simple publicly accessible measure, we proposed an index. DC_{50}, which is the concentration of an agrichemical at which half of the examples of an at-risk species (individual insects or colonies in the case of social insects) are disrupted. This number will be different for each chemical, and can be compared with actual measurements of the chemical in the fields to give a rough-and-ready indication of whether the field is safe or dangerous to biodiversity. Such as measure will be dramatically better than the current kilogrammes per hectare way of measuring

‘dose’.

Whether our approach, or whatever better one may be developed from it, will be adopted is an interesting question. Colleagues have predicted that it will be adopted by pressure groups by rejected by agribusiness. But I am not so sure. If governments showed a willingness to fine companies and farmers for ecological damage, then using a rational and effective framework for measuring potential harm and for calculating how much chemical to apply would be the best way of their staying out of trouble. We need farming of course (in the words of an old car sticker, ‘Don’t criticize a farmer with your mouth full’), but it is not in the interests of farming to cripple essential pollinator species without which there will be no seeds and no crops next year. We all have a common interest in looking after the land that feeds us. I hope our work of the last year or so makes a modest contribution towards this.

Jamie Davies, Edinburgh, July 2022

Our paper:

Connolly CN, Alexander SPH, Davies JA, Spedding M. Environmental pharmacology-Dosing the environment: IUPHAR review 36. Br J Pharmacol. 2022 Dec;179(23):5172-5179. doi: 10.1111/bph.15933. Epub 2022 Aug 16. PMID: 35975296; PMCID: PMC9804906.