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Imidacloprid and the Druckrey-Küpfmüller Equation - The Fundamental Importance of the Nature of Receptor Binding and Associated Adverse Effects

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Editorial

Sánchez-Bayo reported in 2009 that the toxicity of the neonicotinoid insecticides imidacloprid and thiacloprid for arthropods was not only dependent on exposure concentration but also on exposure duration [1]. These dose-response relationships were recognized by Tennekes as a Druckrey-Küpfmüller equation [2], which was first described for the liver carcinogenicity of diethylnitrosamine in rats [3], and is expressed in mathematical terms as:

$$C.T^{n} = \text{constant} \qquad (1)$$

where

C = exposure concentration,

T = induction period of adverse effect, and

n = a time exponent ≥ 1. Haber's Rule is observed when n = 1 [4]

This dose-time-response relationship can be explained theoretically with a mathematical analysis of the kinetics of receptor binding and the associated effect, as shown in Table 1 [5]. This analysis by Druckrey and Küpfmüller is briefly recapitulated.

Reversible receptor binding

When both association and dissociation are fast processes, the equilibrium between toxicant concentration at the site of action and receptor binding (and associated effect) will be established quickly but the effect will also regress quickly. The time course of the effect will be the same as the time course of the toxicant concentration at the site of action. The maximum effect will occur when the toxicant concentration at the site of action is at its maximum. The effects associated with reversible receptor binding will thus be strictly concentration-dependent (Table 1).

Slowly reversible receptor binding

When receptor binding is only slowly reversible, the time to maximum effect will be delayed, and the toxic effect will also be slowly reversible. The slower is dissociation, the longer is the time to maximum effect. Upon repeated exposure in quick succession there will be cumulative effects. Because equilibrium between toxicant concentration at the site of action and receptor binding will be established very slowly, toxicity becomes a process that takes place in time. There will be a latency period (i.e. when small amounts of toxicant are bound to the receptors, but no toxic effects are observed yet) up to a defined effect, which can be shortened, of course, by increasing the concentration of the toxicant at the site of action. The effects associated with slowly reversible receptor binding will not only be concentration-dependent but are also dependent on exposure time.

Irreversible receptor binding

When receptor binding is virtually irreversible, the concentration of bound receptors would be proportional to the integral of the concentration of the toxicant at the site of action over time (Table 1). If, under such circumstances, an exposure concentration is kept constant throughout a study, and, as a result, the toxicant concentration at the site of action remains constant as well, integration yields Haber's rule [4], which states that the product of exposure concentration and exposure duration is constant:

$$C.T=\text{constant} \qquad (2)$$

In many cases toxic effects will only begin to occur as from a certain level of receptor binding. In these cases, a 'threshold' of constant value would need to be introduced for both the administered concentration and the time to effect:

$$(C-C_m)\times(T-T_m) = \text{constant} \qquad (3)$$

Where C_m is a threshold concentration,

T_m a minimum time of response.

For toxicants that follow Haber's rule this would merely imply that the threshold concentration and the minimum time of response are so small as not to produce a measurable error. The effects associated with irreversible receptor binding are concentration- and time-dependent and are an outstanding feature of cumulative toxicity (Table 1).

Irreversible receptor binding asssociated with irreversible effect

If, following irreversible receptor binding, the associated effect would be irreversible as well, the effect would be proportional to the integral of the concentration of bound receptors over time. As inferred earlier with irreversible receptor binding, the concentration of bound receptors would be proportional to the integral of the concentration of the toxicant at the site of action over time. So, in cases of irreversible receptor binding and an irreversible associated effect, the effect would be proportional to the double integral of the toxicant concentration at the site of action over time (Table 1). Integration yields effect as the product of exposure concentration and exposure duration to a power, (i.e. $C.T^2$), with the implication that exposure time will enhance the effect. Irreversible receptor binding associated with an irreversible effect leads to time-reinforced toxicity (Table 1).

Table 1: Theoretical approaches to dose-response relationships according to Druckrey and Küpfmüller [5]

Reversibility of receptor binding	Receptor binding in relation to compound concentration	Reversibility of the effect	Effect in relation to receptor binding	Effect in relation to compound concentration	Dose-response characteristics
$T_R \rightarrow 0$	$C_R \sim C$	$T_r \rightarrow 0$	$E \sim C_R$	$E \sim C$	dose-dependent
		$T_r \rightarrow \infty$	$E \sim \int C_R\, dt$	$E \sim \int C\, dt$	C.t = constant*
$T_R \rightarrow \infty$	$C_R \sim \int C dt$	$T_r \rightarrow 0$	$E \sim C_R$	$E \sim \int C\, dt$	C.t = constant*
		$T_r \rightarrow \infty$	$E \sim \int C_R\, dt$	$E \sim \int \int C\, dt$	reinforced by time

T_R is the time constant for the reversibility of receptor binding.

T_r is the time constant for the reversibility of the effect.

C is the concentration of the compound at the site of interaction with the receptor.

C_R is the concentration of bound receptors.

E is the effect.

* if C remains constant.

Time-reinforced toxicity is easily envisaged with genotoxic carcinogens such as the nitrosamines: Irreversible DNA alkylation by diethylnitrosamine (receptor binding) results in irreversible mutations (associated effect) ultimately causing neoplastic transformation [6]. The Druckrey-Küpfmüller equation explains harmful effects of low exposure levels of a toxicant during prolonged exposure. The lower the exposure concentration, the lower the total dose required for the damaging effect, even though the adverse effect occurs only after a long exposure period.

It is now clear that the theories of Druckrey and Küpfmüller are generally applicable. Non-genotoxic chemicals such as neonicotinoid insecticides and organic mercury show dose-response relationships identical to that of an alkylating N-nitroso carcinogen such as diethylnitrosamine [7,8]. By implication, risk assessments can no longer assume thresholds for non-carcinogens [9]. Contrary to widely held belief, a threshold does not follow automatically from absence of genotoxic potential. For such chemicals, risk management should be based on the ALARA principle ("as low as reasonably achievable"). The use of neonicotinoid insecticides such as imidacloprid in agriculture could cause a catastrophy in the insect world. Imidacloprid is mobile and very slowly decomposed in the soil (half-life 200 days), and may leach into groundwater, or run-off to surface water [10]. In many areas of intensive agriculture, surface water is contaminated with imidacloprid [10], which could make much of the flora extremely toxic to insects.

Mechanism of action confirmed by producer

The identification of the dose-time-response characteristics and mechanism of action of imidacloprid in arthropods [1,2] by Sánchez-Bayo and Tennekes was entirely consistent with mechanistic studies published by the producer of imidacloprid in the 1990s. Bayer scientist Abbink certified in 1991 that "imidacloprid is the first highly effective insecticide whose mode of action has been found to derive from almost complete and virtually irreversible blockage of postsynaptic nicotinic acetylcholine receptors (nAChRs) in the central nervous system of insects" [11]. In 1999, Mehlhorn and Bayer scientists Mencke and Hansen summarized the effects of imidacloprid on the flea Cfenoaephalides felis as follows [12]: "the irreversible blocking of the nACh receptors leads to a lethal hyperactivity of the nerves and muscles of the insect."

Environmental protection

The need to protect the environment and conserve natural resources-is now a value embraced by the most competitive and successful multinational companies [13]. The McKinsey Corporation's survey of more than 400 senior executives of

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companies around the world found that 92 percent agreed with Sony Corporation president Akio Morita's assertion that the environmental challenge will be one of the central issues of the 21st century [14]. If the senior executives of the companies producing neonicotinoids had belonged to this overwhelming majority these insecticides would have been pulled from the market to avoid serious damage to the environment. Quite the contrary is the case.

Mechanism of action revoked by producer

Following the Tennekes publication [2], Maus and Nauen of Bayer CropScience, despite previous assertions by Bayer experts, contested the irreversibility of receptor binding by imidacloprid [15]. They stated that "Similar to acetylcholine (Ach), a neonicotinoid is binding to the nAChRs, and the binding of neonicotinoid insecticides is reversible." Maus and Nauen did not retract earlier publications of Bayer experts [11,12] that had asserted irreversibility of receptor binding, and did not declare a conflict of interest [15]. Similar assertions were made by Cresswell of the University of Exeter [16,17], most recently reasoning as follows: "it appears that imidacloprid does not accumulate locally at its target sites by binding irreversibly to receptors in the insect nervous system. Instead, rapid postexposure recovery is observed in honey bees, and other insects including cockroaches, termites, and bumble bees, which clearly indicates reversible binding". Cresswell, who is known to have received commissions from Syngenta, the producer of the neonicotinoid thiamethoxam, did not declare a conflict of interest [17].

Product defense leading to insect decline

The nature of receptor binding by imidacloprid is of fundamental importance for risk assessment. If, as Bayer and Syngenta-sponsored scientists now infer, receptor binding is reversible, the toxicity of imidacloprid would be concentration-dependent only (Table1), and there would likely be a threshold concentration below which there would be no adverse effects. However, studies of the Universities of Utrecht and Nijmegen showed that the pollution of surface water with imidacloprid quantitatively correlated with decline of invertebrates and insects-dependent bird species [18,19]. Moreover, research in the National Park Dwingelderveld, The Netherlands, and in a nature reserve in Krefeld, Germany, showed that, since the introduction of imidacloprid in the mid-1990's, at least three-quarters of the ground beetles and flying insects have disappeared [10,20].

The fact of the matter is that irreversible receptor binding and associated time-reinforced toxicity resulting from prolonged exposure to infinitesimal imidacloprid concentrations in the environment would explain the observed correlations with decline of invertebrates and insects-dependent bird species [18,19]. Environmental contamination with neonicotinoids appears to be a major factor in catastrophic insect decline observed since their introduction in the mid-1990s. Unwarranted product defense by Bayer and Syngenta may have had catastrophic consequences for the environment.

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