

Aiming for a Better Tomorrow

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Keywords: Biopesticide, Imidacloprid, Insecticide, Insecticide alternatives, Insecticide mortality, Insecticide poisoning, Neonicotinoid.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24628

As per the National Crime Records Bureau India, 43,387 persons committed suicide in 2022 by ingestion of poisons, maximum proportion were of prime working age. Innumerable deaths and hospital admissions are caused by accidental and occupational exposure as well as long-term effects of environmental damage caused by pesticides in India. These ingestions/suicides/exposures also cause loss of a vast number of man days and immense suffering to the families. Neonicotinoids (Neonics) are a newer class of pesticides. They were developed to replace organophosphates and carbamates which were toxic to the environment and to humans. The first one to be launched was imidacloprid introduced by Bayer Crop science in 1980. From 1980 to 2017 imidacloprid has been the topmost selling pesticide in the world.¹ They act primarily on the parasympathetic system and partly on the sympathetic system on the postsynaptic nicotinic acetylcholine receptors (nAChRs) in an agonistic capacity. They have an affinity for $\alpha 4\beta 2$ and $\alpha 7$ receptors in the vertebrate brain but have very little effect on the nicotinic receptors of the peripheral nervous system ($\alpha 1\gamma\alpha 1\delta\beta 1$ subtype).² As they have poor blood-brain barrier penetration in vertebrates they are not supposed to affect humans much. On the other hand, in insects, they act on $\alpha 4\beta 2$ (insect-specific receptor subtype) of nAChRs and as the insects do not have a blood-brain barrier, they are highly effective and selective for them. In a study done by Mohamed et al. an initial fast absorption and high serum levels were found, and the levels remained elevated for 12–15 hours, indicating zero order kinetics were coming into play and the metabolism mechanisms were getting saturated.³ Cytochrome p 450 isoenzymes seem to play a significant role in metabolism. This may also be responsible for variable effects in various individuals depending on their cytochromes. Imidacloprid can be metabolized in one of two ways, one of them is the nitroimine reduction pathway to yield nitroso guanidine, aminoguanidine, and urea imidacloprid by CYP 1A2, 2B6, 2D6, and 2E1 isoenzymes and the other one is hydroxylation and desaturation to 5-hydroxyimidacloprid and imidacloprid olefin by CYP 3A4 isoenzymes. If the person is getting cytochrome enzyme inhibitors simultaneously, the action will be prolonged.

All studies done on patients admitted with acute ingestion have shown mild to moderate symptoms and a mortality rate of 1–2%.^{3,4} In this issue of IJCCM Sanga et al.⁵ have presented a retrospective study of patients getting admitted with acute neonicotinoid toxicity and found that almost a quarter of patients presenting with Neonicotinoid ingestion required ICU admission. First-generation Neonic imidacloprid ingestion in particular has been associated with severe symptoms.

Another significant feature of Neonicotinoids is that they are systemic pesticides and translocate into all parts of treated plants, including pollen, nectar, guttation fluids, and the foods grown by those plants. They have been found in soil, dust, wetlands,

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How to cite this article: Kharbanda M. Aiming for a Better Tomorrow. *Indian J Crit Care Med* 2024;28(1):11–12.

Source of support: Nil

Conflict of interest: None

groundwater, nontarget plants and vertebrate prey.⁶ Lately many red flags have been raised about the environmental effects and long-term effects on mammals as well as humans. The $\alpha 4\beta 2$ nAChR affected by neonicotinoids, is found in the highest density in the thalamus. The change in density of this particular receptor has been implicated in various disorders like schizophrenia, depression, Alzheimer's and Parkinson's disease.⁷ In the developing brain, this subtype is involved in neural proliferation, apoptosis, migration, differentiation, synapse formation, and neural circuit formation.⁸ Marfo et al. compared urinary N-desmethyl-acetamiprid (DMAP) which is a metabolite of imidacloprid levels of a small group of patients with new onset neurological symptoms recent memory loss, finger tremor, and more than five of six symptoms (headache, general fatigue, palpitation/chest pain, abdominal pain, muscle pain/weakness/spasm, and cough) with controls. Detection of DMAP was associated with increased prevalence of the symptoms (odds ratio: 14, 95% confidence interval: 3.5–57).⁹ It has also been associated with tetralogy of Fallot in a population study in USA.¹⁰

In 2016, a law was passed by the French government banning the use of the five neonicotinoids previously authorized: clothianidin, imidacloprid, thiamethoxam, acetamiprid and thiacloprid. The ban happened as they were found to be at least partially responsible for colony collapse disorder (CCD) syndrome in honeybees.¹¹ When most of the worker bees in a honeybee colony vanish, it is called CCD syndrome. This leaves only a queen, some food, and a few nurse bees to look after the young bees that are still developing. They have also been found to have harmful effects on fitness and life span of wild bees and bumblebees.¹² These bees are extremely important as pollinators for various crops and other plants. Pollinators give essential services to agriculture and the ecosystem. The reduplication of nearly 85% of the world's flowering plants and the product of 35% of the world's food crop depends on pollinators. Considering this, the European union has also banned many neonicotinoids which were being used in crops earlier. In an expert assessment conducted by the French agency for food, environmental and occupational health and safety, lesser

toxic alternatives to the banned neonicotinoids were available for 80–90% of recognized uses.¹³

Pesticides have 2 timelines of effect on humans, one is the acute accidental exposure/ingestion of pesticides and the second is the cumulative effect on the environment and humans due to the pesticides seeping into the food, water and soil. For this reason, the trend is shifting towards Biopesticides.

Biopesticides are defined by the Environmental Protection Agency of the USA as “Certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals”.¹⁴

They may be classified into three types:

1. Naturally occurring substances that control pests by nontoxic mechanisms are called Biopesticides. They may be various Semiochemicals also. (When one organism makes a chemical signal that affects the behavior of another organism of the same kind or a different kind, it is called a Semiochemical). They may interfere with mating such as sex pheromones of insects or plant extracts attracting insects into traps.
2. When microorganisms (e.g., a *bacterium*, *fungus*, *virus* or *protozoan*) act as the active ingredient, they are called microbial pesticides, e.g., a *fungi* killing weeds or insects.
3. Pesticidal substances that plants produce from genetic material that has been added to the plant are called Plant-Incorporated-Protectants (PIPs). As an, e.g., Plant-producing *Bacillus thurensis* protein kills larvae of insects.

Biopesticides have several advantages. Viz:

- They are inherently less toxic than conventional synthetic pesticides.
- They decompose quickly and are required in a lesser amount, leading to lesser environmental exposure and pollution. They affect only the target organisms and related organisms, unlike the conventional pesticides which are broad spectrum and can affect widely differing organisms such as plants, insects, birds, and mammals.
- They can greatly reduce the use of conventional pesticides and can be used as part of integrated pest control programs.

In India as compared to other developed countries a lot of conventional pesticides like organophosphates, organochlorines, and first-generation Neonicotinoids like imidacloprid are used, leading to a large number of fatalities by suicidal ingestion as well as accidental exposure apart from difficult-to-quantify effects of chronic exposure like effects on pollinators and effects of chronic ingestion via environmental pollution on birds, animals and humans. As India is trying to leapfrog into becoming a developed country and improving the quality of life of our citizens, we should also be serious about removing the hazards and risks to our people because of pesticides. Although a lot of work has been done by the Department of Agriculture and Farmers Welfare (DA and FW), the Ministry of Agriculture and Farmers Welfare to review the registration of various harmful pesticides, and many hazardous chemicals have been banned. The promotion of biopesticides is also the Government's official stated policy and integrated pest control programs for various crops have been designed. Karunaratne et al. have shown that banning hazardous pesticides can lead to decreased suicidal mortality by ingestion of pesticides.¹⁵ Although Neonicotinoids are a better option than the earlier pesticides, the long-term effects are still not fully known, and this seemingly innocuous chemical has the possibility of leading to long-term damage to the environment

and humans. India needs to do a continuous review of alternatives to the present hazardous chemicals being used to decrease the risk to our citizens so that we can look forward to a better tomorrow.

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