PAN Europe

Pesticides Action Network Europe

Endocrine disrupting pesticides: concerns about vinclozolin and procymidone

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This briefing explains some of the scientific concerns about the effects of two endocrine disrupting chemicals (EDCs), in a moment where they are in the pipeline to be re-approved under the EU Pesticides Authorisation Directive. The approval of pesticides with endocrine disrupting properties is a good example of why current EU risk assessment fails to protect human health and the environment (see PAN Europe Briefing No 2 *Why current European pesticide legislation fails to protect our health*) and why we need to improve legislation (see also our position paper on EU Pesticides Authorisation).

Wealth of new scientific knowledge on endocrine disruption

After the discovery that endocrine disruption by synthetic chemicals discharged into the environment is a general phenomenon in our world (1) many scientists have been studying endocrine disruption and have been elucidating the mechanisms of disruption involved. All living organisms depend upon a large and intricate array of chemical signalling systems to guide biological development and regulate cell and organ activity. Endocrine disrupting chemicals (EDCs) are chemicals that can disrupt this signalling system and interfere with thyroid hormones, male (androgens) and female (oestrogens) sex hormones and other products of endocrine processes.

The effects of EDCs on developing organisms are of greatest concern, since many of the disruptive effects on developmental exposure tend to be permanent and irreversible. Research on endocrine disruption during different stages of development, particularly during foetal life, focuses on effects which may develop later in adult life such as obesity, heart disease, diabetes, decreased fertility, impaired immune function and neurological deficits. Development of the young has also been found to be impaired. Evidence for endocrine disruption is overwhelming in nature (alligators and polar bears with reproduction problems; deformations of frogs and tadpoles) (2). In humans it is clear that significant exposure to tens to hundreds of EDCs is a fact given the 'body burden' analyzed in blood serum and mother's milk (3). Dutch studies of PCBs and dioxins shown that low parts per billion concentrations of these contaminants impair cognitive (4), immune system development (5) and play behavior (6). Low doses and the moment of exposure (during development) appear to be the key determinants in studying endocrine disruption.

Current risk assessment has a blind spot for endocrine disruption

Traditional WHO/FAO – Codex Alimentarius – and other risk assessment systems for toxins used in the past 30 years focused on the healthy male, looking at endpoints like gene mutations, damage to organs, weight loss and death at (very) high doses, typically part *per* millions and parts *per* thousand level. New data suggest that extremely low doses of EDCs (parts *per* billion or lower) can cause measurable and highly significant endocrine disruption. Estradiol levels act between 0.1 and 100 part *per* trillion in breast cells, leading to gene activation (7), a concentration region never reached in conventional toxicology dose-response curves. Testing EDCs at only very high doses is likely to miss signal-disrupting events that can be expected to occur at much lower levels of exposure. For instance, plant-derived oestrogens at low doses inhibit aromatase enzymes but at higher doses inhibit mammalian oestrogens. Dose-response curves for EDCs could give one response in the 'physiological range' of parts *per* billions and give another response (like cell death) at the high 'toxicological range' of parts *per* million/thousand (8). A US Environment Protection Agency (EPA) peer-

review committee on low-doses concluded that the testing paradigm used for assessment of reproductive and developmental toxicity should be revised (9).

Another important aspect that is missing in traditional risk assessment is the special vulnerability of children and the unborn. In the foetal stage hormones play an essential role in the 'lay-out' of the organism and disruption can lead to permanent failures in adulthood. Children and the unborn are more vulnerable than adults (children having, for instance, no closed blood-brain barrier up to six months old). Special 'windows of vulnerability' are postulated (10) and have been demonstrated for the insecticide chlorpyriphos (11), a neurotoxic chemical acting on brain development.

Combination effects of the many EDCs present in the environment is something that has to be taken into account. One recent study (12) clearly shows that weak oestrogenic chemicals combined produce significant mixture effects. Combinations of pesticides, but also chemicals in pesticide formulations, like the EDC nonyl-phenol, as common ingredient should be taken into consideration.

Many pesticides are associated with endocrine disruption

The currently best-known case of endocrine disruption among pesticides is probably atrazine, a herbicide causing birth deformation in amphibians at very low doses in the ppb-range. Atrazine demasculinized frogs above 0.1 ppb (13), concentrations found regularly in the environment and drinking water. Numerous studies in laboratory animals have shown that a series of pesticides is involved in endocrine disruption (14). Effects like reduced fertility, poor semen quality, more feminine play behavior, genital abnormalities, *etc.* seen in wildlife studies will be the kind of effect evaluation bodies will have to look at as a specific endpoint for endocrine disruption. Epidemiological studies point in the same direction of subtle and easy to miss effects (15) on brain development (coordination and memory problems) in Mexican children exposed to pesticides in early life. Dutch scientists discovered a disturbed boy-girl birth proportion in fruit growers (16). Poor semen quality was demonstrated in Dutch farmers (17) spraying pesticides on regular basis. Statistical relations between exposure to pesticides and poor semen quality in males in Minneapolis have been shown (18). Taken together there is evidence that endocrine disruption by EDCs, including pesticides, is already influencing health of humans and wildlife negatively. Precautionary action should be the answer.

Concerns about vinclozolin and procymidone

Vinclozolin is a protectant non-systemic dicarboximide fungicide used mainly on oilseed rape and peas in the UK (19), and on vines, fruit and vegetables worldwide (20*)*. It was first introduced by BASF in Germany in 1976 and is sold under a number of trade names including Ronilan and Flotilla.

In 1998 23.4 tonnes were used on 80,574 ha of oilseed rape in the UK (21) and approximately 64 tonnes in total in the US (22) in 1999 on a wide variety of crops.

Procymidone is a protectant systemic fungicide used mainly on vines, vegetables, ornamentals, cereals, sunflowers, oilseed rape, soy beans, peanuts and tobacco. It was first introduced by Sumitomo Chemical in 1976 and is sold under a number of trade names including Sumilex and Promidone (20).

Acute toxicity

Vinclozolin is not acutely toxic, and is classified by the World Health Organisation as Class III "unlikely to present acute hazard in normal use" (23*)*. The acute oral LD50 (the dose required to kill half a population of laboratory animals) is more than 10,000 mg/kg for rats. It is an irritant to skin and may cause sensitization (19). Procymidone is also not acutely toxic. The acute oral LD50 is 6,800 mg/kg for male rats (20).

Chronic toxicity

A review of vinclozolin by the US Environmental Protection Agency (22) has concluded that the chemical and/or its breakdown products are associated with the development of testicular tumours in rats, and the final breakdown product of vinclozolin in the rat is also thought to be carcinogenic.

Tests on dogs have shown effects on the kidney and prostate glands. It is suggested they are the most sensitive species (24).

Reproductive toxicity

Issues over the reproductive toxicity of vinclozolin have driven regulation for over a decade. The UK Advisory Committee on Pesticides (ACP) has kept vinclozolin under review since 1991 (25) following reports of the reproductive effects of the chemical on rats, to assess the risk to consumers and operators. The specific concerns were that vinclozolin could feminize rats and could also damage reproductive capacity in rats. Given that the chemical could be used by operators on a regular basis over quite considerable periods of time, and that a short exposure could have serious consequences for a 'susceptible' individual, and a high proportion of women were employed in the horticultural sector, action was needed. Approvals for use on strawberries, lettuce, tomato and raspberries were all suspended. Regulatory action was taken to reduce exposure to both by requiring tractor-mounted or trailed downward placement by hydraulic sprayer. Protective clothing requirements were also made. Further data was submitted to the ACP in 1995, when uses in apple orchards were reinstated provided that the operator was protected by having air filtration fitted in the tractor cab (26).

In 1999, during the EU review of the toxicity of vinclozolin, the European Commission Scientific Committee on Plants was asked to consider if humans, and particularly children, might be more sensitive than rats to its effects. The Committee said humans were not more sensitive than animals, and that it was unlikely that a single exposure could cause ill effects. It also considered that the mechanism of toxicity was now established. It did, however, note that adverse effects on young animals were generally irreversible, whereas effects on adult animals could generally be reversed (27).

In the meantime, the US EPA considers vinclozolin to be an endocrine-disrupting chemical interfering with lipid metabolism and/or storage and inducing reduced sperm count, decreased prostate weight and delayed puberty in test animals (22). A further question emerging from the EPA review is whether vinclozolin shares a common mechanism of toxicity with the fungicides procymidone and possibly iprodione, and what might be the likely impact of additive exposure. A recent scientific study from the US EPA suggested already a cumulative effect between vinclozolin and procymidone, as anti-androgens sharing a common androgen receptor mediated mechanism of action. The conclusions of this study will be instrumental in setting cumulative risk assessment for these substances in the future (28).

In 2000, the European Commission (29) has also indicated vinclozolin as a high priority chemical for investigation of endocrine effects, and the UK Department of the Environment, Transport and the Regions (30) has echoed these concerns.

In a recent study the conclusions on transgenerational actions of vinclozolin in rats' male fertility offers further reasons for concern (31). Four generations of male offspring from vinclozolin treated mothers were examined, with reduction in sperm quality and quantity observed in all generations with comparable severity. In addition, 8% of the male offspring in each generation were completely infertile.

Although procymidone is listed in the Commission Communication on the Implementation of the Community Strategy for Endocrine Disruptors as a substance with insufficient data, this report was recognised as a starting point in a priority setting exercise (32). Later, procymidone was recognised as one of the substances with high exposure concern and with evidence of endocrine disrupting properties listed in the Commission working document on the implementation of the Community Strategy for Endocrine Disruptors (33). There is indeed matter for concern. Results from a recent study conducted in South Korea indicate that procymidone may act as a stronger androgen receptor antagonist in male rats when compared to known endocrine disruptors such as vinclozolin, linuron, or p,p'-DDE (34).

Environmental fate

Vinclozolin is only partially broken down by soil microorganisms, with estimated half lives of three days to more than three weeks depending on soil type. Field data indicate it will be strongly sorbed to moist soils and unlikely to leach significantly (26). Procymidone persists in soil for 4 to 12 weeks, depending on humus content (20).

Wildlife
There has been concerns about the possible impacts of vinclozolin on birds. The question was put to the EU's Scientific Committee on Plants and received the answer that under the conditions of use of vinclozolin in orchards, vineyards and fields there would be no unacceptable risk to wild mammals. While short term effects on birds and wild mammals would not be expected, possible long term effects on birds could not be excluded (35). Vinclozolin is said to present a minimal hazard to bees when used as directed, but users are advised to 'consider informing local bee-keepers if intending to spray crops in flower' (19). It is labelled in the UK as harmful to fish and aquatic life. The US review notes chronic risk to aquatic organisms has not been assessed due to lack of data.

Food residues
Detectable levels of residues of vinclozolin and procymidone are consistently found in European fruits and vegetables. In 2002, 11% of all bean and 2% of all carrot samples were found contaminated with detectable levels of vinclozolin. Similarly, 13% of all pears, 5% of all peach and 4% of all bean samples were found contaminated with detectable levels of procymidone. Procymidone was the ninth most frequently reported pesticide (36).

Final remarks
Despite the concerns echoed by the scientific community regarding EDCs, the EU is failing in providing an adequate legislative framework. The Community Strategy for Endocrine Disrupting Chemicals *per se* does not hold enough strength to influence the removal of these substances from the market. On the other hand, the current risk assessment in the pesticides authorisation Directive (Directive 91/414/EC) does not take into consideration the exposure to small doses or vulnerable groups such as children and the unborn. Future pesticides regulation should be based on the highest protection level available in line with the precautionary principle. Active ingredients (including their metabolites) that meet the criteria for human toxicity carcinogenic, mutagenic, toxic to reproduction, sensitizing or endocrine disrupting, should not be authorised in the EU market.

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PAN Europe, Development House, 56-64 Leonard Street, London EC2A 4JX, UK
Tel +44 (0) 207 065 0920 Fax +44 (0) 207 065 0907
Email: sofia-paneurope@pan-uk.org Webpage : www.pan-europe.info

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