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Developmental disorders induced by pesticide degradation products

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Concluding Remarks

Pesticides are designed to chemically control undesired organisms in agricultural ecosystems and hence their behavior in all steps of intended use on the fields and unintended distribution (e.g. in water) has to be considered. It was hypothesized in this thesis that degradation products provoke adverse effects on aquatic biota that differ from specific effects of the parent pesticides. The aim of this thesis was therefore to analyze the effects of environmentally stable pesticide degradation products on fundamental processes in a living organism, like growth and development. Here, I review the findings on a limited series of compounds, the chloroacetanilides, the formamidines and their degradation products, and a limited series of biological tests in order to analyze the chain of effects from pesticide application to adverse environmental effects. A risk to the environment and to man has been indicated and this has prompted a remark on the regulation of pesticides.

Pesticide degradation products

The pesticide's environmental persistence (half-life), transformation pathways and the transformation products vary with environmental conditions (Webster *et al.* 1998; Graham *et al.* 2000). The massively applied chloroacetanilides and formamidines break down to compounds that are persistent in the environment, indicating a probable long-term hazard (Konopka 1994; Stamper and Tuovinen 1998; Scribner *et al.* 2000). The degradation products are generally more water-soluble and are easily translocated into other environmental compartments, thus extending the areas that are potentially at risk of the pesticides. This latter problem could be mitigated by improved soil adsorption properties and agricultural management practices. For instance, reduced soil erosion and increased organic matter content would reduce dissipation of the pesticides and their degradation products (Farenhorst and Bowman 2000). In the temperate region, due to the longer lapse of time after application of the pesticides, surface waters receive pesticide degradation products, which get distributed as far as in the river mouth (Steen *et al.* 1999). The tropical environment confers ecotoxicological risks to pesticides that differ from that in the temperate regions. The role of the degradation products is more prominent in the tropics than in the temperate regions (Lalah and Wandiga 1996; Karlsson *et al.* 2000). The relatively higher ambient diurnal temperatures

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and UV irradiation in these regions favor microbial degradation, hydrolysis and photolysis of the pesticides, thereby decreasing their persistence, while increasing the concentrations of their degradation products in the environment. It is concluded that although degradation products of pesticides receive a growing scientific attention, their role in ecotoxicology is still inadequate.

Specificity of Pesticide degradation products

Toxicity of pesticides is governed by their bioavailability and reactivity at the target sites (Hansch and Fujita 1963). Both the bioavailability and the interaction with the target change upon the degradation of the pesticides. Bioavailability of most organic compounds to the cells of living organism is dependent on their lipophilicity, expressed usually as the $\text{Log } K_{ow}$ and their baseline toxicity (narcosis) can be predicted by this factor (Roghair *et al.* 1994; Cronin and Dearden 1995; Vaes *et al.* 1998). The toxicity of aniline based pesticides and their degradation products to *Chironomus riparius* larvae in the present study (Chapter 3) also met this relationship.

During the manufacture of pesticides, carriers are incorporated to enhance the pesticides availability or to slow down their release. In the environment bioavailability of pesticides and other toxicants is influenced by several factors, including their water solubility; for example in the present study the lower water solubility of amitraz prevented its toxicity to the aquatic *C. riparius* (Chapter 3). Bioavailability of pesticides is also influenced by the presence and nature (aromaticity) of the organic matter (Farenhorst and Bowman 2000; Ahmad *et al.* 2001), UV irradiation-aided weakening of adsorption bonds (Bossan *et al.* 1995; Wernersson *et al.* 2000) and temperature-governed increased plant uptake (Kiflom *et al.* 1999), which could enhance exposure of grazers through ingestion, for example in the case of paraquat toxicity to frog larvae (Dial and Dial 1995). All in all, transformation of the pesticides lowers their $\text{Log } K_{ow}$ and hence their lipophilicity. Can this change be construed with diminished hazard or does the transformation alter the specificity of the compounds?

Specificity of pesticide's reactivity on the target organisms is exploited in their design and manufacture. The formamidines mimic monoamine oxidase in invertebrates, thereby inhibiting the enzyme (Aziz and Knowles 1973), while the chloroacetanilides inhibit photosynthesis in

selected species of plants. Upon degradation this selective toxicity to target species is lost and their lethal toxicity to non-target species is also generally reduced. By applying a battery of 4 test systems, this thesis has shown that transformation of the pesticides give them new toxic properties. The more polar aromatic amine degradation products elicit toxicity by a mechanism that is different than narcosis in the *V. fischeri* (Hermens *et al.* 1985; Vaes *et al.* 1998). In the present study the degradation products were more toxic than their corresponding parent compounds to the bacteria (procaryote), even though their Log K_{ow} values were lower. The opposite was true in the animal species (eucaryote) (Chapter 3). This thesis shows that while the simple QSAR approaches could be a useful tool in prediction of toxicity of untested compounds that act by narcosis, it can be seriously in error in predicting toxicity that is governed by mechanisms different than narcosis (Chapter 3). In the frog developmental studies the predominant type of aberration caused by the parent compounds were edema, which is typical of cell membranes and hence osmoregulation disruptions, while the degradation products exhibited diverse types of aberrations (Fig 2, Chapter 4; Chapter 5). The teratogenicity expressed as the ratio between LC50 to EC50 of the pesticides was enhanced upon degradation; for example the concentrations of 2,4-dimethylaniline that induced 100% malformation proved non lethal to embryos (Chapter 5). In view of their diversified specific toxic effects established in the present study, the seemingly innocuous degradation products could underlie long-term hidden risks of the pesticides in the environment.

Developmental disorders

Could the role of the pesticide degradation products in the etiology of developmental malformation help to understand the epidemiology of increased frog malformation and the dwindling of amphibian species (Wake 1991; Blaustein and Wake 1995; Burkhart *et al.* 2000)? The long list of environmental factors identified as possible cause of frog abnormalities has underrated the pesticide degradation products (Chapter 3-5). This list includes antithyroid compounds, mineral (Ca and Mg) depletion, surfactants, nitrate fertilizers, parasitic trematodes, petroleum products, metals and UV radiation, besides other numerous anthropogenic environmental teratogens (Davis *et al.* 1981; De Zwart and Sloof 1987; Blaustein and Wake 1995; Fort *et al.* 1999; Schuytema and Nebeker 1999; Burkhart *et al.* 2000; Mann and Bidwell 2000). The widespread use of

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pesticides, especially the chloroacetanilides, in the agricultural fields makes them important contaminants of the amphibian habitat, which could be teratogenic as was demonstrated in this study (Chapter 4-5).

The fact that the pesticides studied here, chloroacetanilide and formamidine degradation products, were found to be genotoxic (Chapter 3) and form DNA adducts (Bonfanti *et al.* 1992; Nesnow *et al.* 1995) raises the question on the possible ramification of this scenario in a developing embryo. The compounds in the present study exhibited a predilection for specific organs or system of the embryos. 2,4-dimethylaniline, for instance, caused depigmentation and encephalomegaly, both representing the nervous system effects and paraquat retarded tail growth of the larvae (Chapter 5). There are several human developmental disabilities, whose etiologies are not well understood and there are also a number of chemicals and pesticides that have not yet been evaluated for their teratogenic potential (Goldman and Koduru 2000). The assay with the *Xenopus laevis* embryos is reported to be able to predict 85% of the human teratogens (Dumont *et al.* 1983; Courchesne and Bantle 1985; Sabourin *et al.* 1985; Dawson and Bantle 1987; Sabourin and Faulk 1987; Bantle 1995). Therefore, the degradation products of chloroacetanilides and formamidine pose potential health risks to man.

Environmental Regulation

This study underlines the need to consider pesticide degradation products in regulating pesticide use. I have demonstrated the presences of diverse toxicity endpoints of pesticides and their degradation products and therefore propose a more diverse evaluation of toxicity in the current regulatory process. This thesis has shown that degradation of a pesticide could attenuate its lethal toxicity while conferring on it risks of genotoxicity or teratogenicity (Chapters 3-5). Such risks could be hidden and on a long-term scale they could even bear far-reaching effects on a species leading to near extinction as was experienced with the effects of organochlorines on top predators in the sixties. These risks may be underrated in the current admission policies that characterize the pesticides based on the toxicology of the parent compounds mostly. Therefore, the extra costs required in identifying and quantifying toxic effects and in accommodating degradation products is justified and a revision of environmental monitoring and quality criteria is appropriate.

Setting up risk assessment for application in regulations on pesticides is currently dogged by inadequate toxicological data (Steen *et al.* 1999), and this is worse for the degradation products (Belfroid *et al.* 1996). The transformation of pesticides follows varied pathways and results in diverse products, most of which cannot be detected with sufficient reliability (Belfroid *et al.* 1996). The coupled processes of sorption and degradation of the pesticides and their degradation products are indeed varied making it difficult to come up with a simple fate model to be used in the risk evaluation procedures. Certainly, not all degradation products are environmentally stable. Thus a first step could be to identify the environmentally stable degradation products and determine their adverse biological effects, as in the present study, in order to incorporate them in the chain of effects assessment.

Formulation of environmental protection legislation is still at its inception stage in Kenya (GOK 1999). Environmental assessment and monitoring mostly rely on World Health Organization or European Union standards. These are inadequate given the unique environmental conditions in Kenya. To give an example from the present study: the absence of herbicide residues from water and sediment would suggest that the application was safe, while the abundance of the degradation products indicated the contrary. To achieve the global 2020 vision of sustainable development and nutrition for all, formalized by Kenya (Republic of Kenya 1997), it is imperative that Kenya regulates pesticides according to a new advanced standard and avoid the mistakes that marked earlier agro-industrial revolutions in the North and produced unwholesome environments.

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