TOXICOLOGICAL HIGHLIGHT

Developmental Toxicity of a Triazole Fungicide: Consideration of Interorgan Communication

Nikolay M. Filipov and David A. Lawrence

Wadsworth Center, New York State Department of Health, P.O. Box 509, Empire State Plaza, Albany, New York 12201–0509

Triazole fungicides, which exhibit their antifungal activity by inhibiting fungal ergosterol biosynthesis, are economically important agricultural chemicals as they are widely used on crops such as wheat, barley, and orchard fruits (Buchenauer, 1987). However, in spite of their widespread use, toxicity evaluations have been performed only within regulatory submission requirements for many of the triazole fungicides. Comprehensive data assessing their biological effects has been very limited, and in the case of certain triazole fungicides (e.g., tebuconazole), almost completely lacking. Moreover, data addressing possible adverse effects of triazole fungicide exposure during development is even more limited. When developmental exposure data is available, it pertains predominantly to the teratogenic potential of selected triazole fungicides such as cyproconazole (Machera, 1994).

Considering the importance of pesticide exposure during development (NRC, 1993) and in particular, the sensitivity of the nervous, immune, and reproductive systems to changes in the environment, Moser et al. conducted a comprehensive developmental exposure study with one of the triazole pesticides, tebuconazole. The outcome of this endeavor demonstrates the feasibility of such studies and their capability for detecting relatively specific adverse effects caused by chemical exposure. Tebuconazole exposure was associated with impaired performance in the Morris Water Maze learning task (a hippocampally mediated spatial learning task). This learning deficit correlated well with neuropathological findings (i.e., pyknotic cells and pyramidal cell loss in the hippocampal fields). Due to the relative absence of consistent effects of tebuconazole exposure on reproductive and immune end points within the battery of tests that were performed, the authors rightfully classified this triazole fungicide as a potential neurotoxicant specifically targeting the hippocampus.

When adult rats were acutely exposed to 14 different triazole fungicides in a structure-activity relationship (SAR) analysis, only triadimefon and its metabolite triadimenol caused a transient increase in hyperactivity (measured in figure-eight mazes) and stereotyped behavior, whereas tebuconazole, among other triazoles, did not produce this effect (Crofton, 1996). Based on this finding, Crofton (1996) suggested that hyperactivity might be used as an exclusion criterion in the design of future triazole fungicides. Certainly, within the context of adult acute exposure with hyperactivity as the neurotoxic outcome, this was a sensible suggestion. Moser et al., however, clearly demonstrate that in a developmental exposure paradigm, tebuconazole is effective in causing a learning impairment. Thus, it could be concluded that: (1) a particular triazole fungicide may not produce an effect in adults, but may lead to neurotoxicity (and possibly other toxic outcomes) when the exposure occurs during development, (2) developmental exposure studies are highly necessary for the full toxicological assessment of triazole and other pesticides, and (3) in neurotoxicity SAR studies with triazole fungicides, multiple end points are necessary.

The study of Moser et al. has contributed to the understanding of the toxicity of tebuconazole by taking into account effects during development. Although it was not “showcased” by the authors, it is equally important that this study could be a guide set for future experiments addressing pertinent fundamental questions related to toxicity of tebuconazole, triazole fungicides in general, and other environmental agents, with regard to multiple organ system analyses. An interesting finding by Moser et al. was the fact that acquisition of learning in male rats was compromised for a longer duration compared to their female counterparts. Similarly, only male rats had increased spleen weight and an alteration (increased T cell:B cell ratio) in the percentage of lymphocyte populations in the spleen. Considering that the hippocampus receives a profound hormonal input (excluding the hypothalamus, the highest of all brain structures) and is very sensitive to its surrounding hormonal milieu during development (Lathe, 2001), that many
Environmental contaminants act in a “stressor-like” manner, ultimately leading to disruption of the otherwise finely tuned neuro-endocrine-immune circuitry (Lawrence and Harry, 2000), and that no hormonal/cytokine analyses, including alterations of hippocampal receptor expression/binding characteristics, were performed by Moser et al. (due to the standardized tests that their study utilized), one could envision experimental paradigms with extended end points that would appropriately address the apparent sex-dependent difference in the hippocampal deficits following tebuconazole exposure during development. Moreover, the increased liver weights observed by Moser et al., which may potentially be associated with increased secretion of factors that are known to affect learning and memory such as certain cytokines (Lathe, 2001), could also be factored into future experimental designs. It is important to note that in addition to the hippocampus receiving hormonal and cytokine input from the endocrine and immune systems, early effects on the brain (hippocampus and hypothalamus in particular) can modulate these peripheral systems (i.e., neuro-endocrine-immune communication is multidirectional; Madden and Felten, 1995; Merrill and Jonakait, 1995). An example of this is neonatal modulation of the hypothalamic-pituitary-adrenal axis, which influences adult immune reactivity (Shanks et al., 2000). Thus, in addition to sex-related hormonal and cytokine differences that might have contributed to the greater learning deficit in the male compared with the female rats, differential hippocampal abnormality might result in functional endocrine and immune alterations. In a way, the work of Moser et al. with tebuconazole, together with data from similar comprehensive studies, could be viewed as a foundation and direction for future mechanistic studies that would attempt to tie together in a meaningful way all the different changes observed in screening tests. However, such analyses will require evaluation of multiple regulatory factors that have interorgan effects, e.g., neuropeptides, cytokines, and hormones.

Typically, comprehensive studies such as the one highlighted here assess the toxic potential of a single pesticide in the battery of tests. Recently, however, attention has focused on the detrimental effects following exposure to more than one pesticide, particularly when the possibility for concomitant exposure is likely to occur in the environment. For example, concomitant adult exposure to the herbicide paraquat and the fungicide maneb, but not to either pesticide alone, resulted in Parkinson’s disease-like abnormalities (Thiruchelvam et al., 2000). Early studies indicated that a triazole fungicide, amitrole, enhances paraquat toxicity in adult animals (Barabas et al., 1980). There is very limited data regarding developmental effects of pesticide mixtures, and complete lack thereof for mixtures containing triazole fungicides. In light of the interactive effects observed in adult animals and possibly greater sensitivity to combined pesticide exposure during development, it is imperative that such studies be considered.

In summary, the study by Moser et al. detects a hippocampal deficit following perinatal tebuconazole exposure. Because tebuconazole was found to be largely without effect in a particular adult exposure neurotoxicity paradigm, the importance of developmental studies in toxicity assessment is highlighted. Furthermore, this study exemplifies the necessity for mechanistic, multidimensional studies that will address toxicant effects on interorgan/system communication.

REFERENCES


