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The use of developmental neurotoxicity data in pesticide risk assessments

Kathleen C. Raffaele [a,*], Jess Rowland [b], Brenda May [b], Susan L. Makris [a], Kelly Schumacher [c], Louis J. Scarano [d]

[a] Office of Research and Development, U.S. Environmental Protection Agency, MC-8623P, 1200 Pennsylvania Ave., Washington, DC 20460, United States
[b] Office of Pesticide Programs, U.S. Environmental Protection Agency, MC-7509P, 1200 Pennsylvania Ave., Washington, DC 20460, United States
[c] Region 7, ENSV/EAMB, U.S. Environmental Protection Agency, 901 N. 5th St., Kansas City, KS 66101, United States
[d] Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, New England Regional Laboratory, 11 Technology Dr., North Chelmsford, MA 01863, United States

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ABSTRACT

Following the passage of the Food Quality Protection Act, which mandated an increased focus on evaluating the potential toxicity of pesticides to children, the number of guideline developmental neurotoxicity (DNT) studies (OPPTS 870.6300) submitted to the U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) was greatly increased. To evaluate the impact of available DNT studies on individual chemical risk assessments, the ways in which data from these studies are being used in pesticide risk assessment were investigated. In addition, the neurobehavioral and neuropathological parameters affected at the lowest observed adverse effect level (LOAEL) for each study were evaluated to ascertain whether some types of endpoints were consistently more sensitive than others. As of December 2008, final OPP reviews of DNT studies for 72 pesticide chemicals were available; elimination of studies with major deficiencies resulted in a total of 69 that were included in this analysis. Of those studies, 15 had been used to determine the point of departure for one or more risk assessment scenarios, and an additional 13 were determined to have the potential for use as a point of departure for future risk assessments (selection is dependent upon review of the entire database available at the time of reassessment). Analysis of parameters affected at the study LOAELs indicated that no single parameter was consistently more sensitive than another. Early assessment time points (e.g., postnatal day (PND) 11/21) tended to be more sensitive than later time points (e.g., PND 60). These results demonstrate that data generated using the current guideline DNT study protocol are useful in providing points of departure for risk assessments. The results of these studies also affirm the importance of evaluating a spectrum of behavioral and neuropathological endpoints, in both young and adult animals, to improve the detection of the potential for a chemical to cause developmental neurotoxicity.

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1. Introduction

The National Research Council report entitled *Pesticides in the Diets of Infants and Children*, released over fifteen years ago, addressed public concerns regarding the possibility that exposure to pesticides (or other environmental chemicals) might cause adverse effects in children [28]. As one major focus, the report evaluated the potential for increased susceptibility of children to some types of adverse health effects. In addressing concerns such as those raised by the report, the U.S. Congress passed the Food Quality Protection Act (FQPA) in 1996; this law required that pesticides be more specifically assessed for their potential to cause toxicity in infants and children and mandated that pesticide risk assessments produced by the U.S. Environmental Protection Agency (EPA) use an additional safety factor in cases where there was uncertainty regarding effects in those age groups.

Use of the standardized EPA Developmental Neurotoxicity (DNT) test guideline (OPPTS 870.6300; [38]), which was finalized in 1991 and slightly revised in 1998, was limited prior to the passage of the FQPA. The guideline includes detailed neurobehavioral and neuropathological assessments of rat offspring following *in utero* and postnatal exposure to a chemical of concern (see Fig. 1) and is similar to a recently finalized international Organization for Economic Cooperation and Development, (OECD) DNT Test Guideline (TG 426) [29]. In 1999, in response to the increased focus on developmental toxicity following the passage of FQPA, the EPA Office of Pesticide Programs (OPP) requested that DNT studies be conducted for many pesticide active ingredients and specifically required (via a "data call-in") DNT studies for all previously registered organophosphate pesticides [39]. Since that date, there has been a large increase in the number of DNT studies submitted to OPP (see Fig. 2).

* Corresponding author. Present address: National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Mail Code 8623P, 1200 Pennsylvania Ave., NW, Washington, DC 20460, United States. Tel.: +1 703 308 7255; fax: +1 703 347 8692.
E-mail addresses: raffaele.kathleen@epa.gov (K.C. Raffaele), rowland.jess@epa.gov (J. Rowland), may.brenda@epa.gov (B. May), makris.susan@epa.gov (S.L. Makris), schumacher.kelly@epa.gov (K. Schumacher), scarano.louis@epa.gov (L.J. Scarano).

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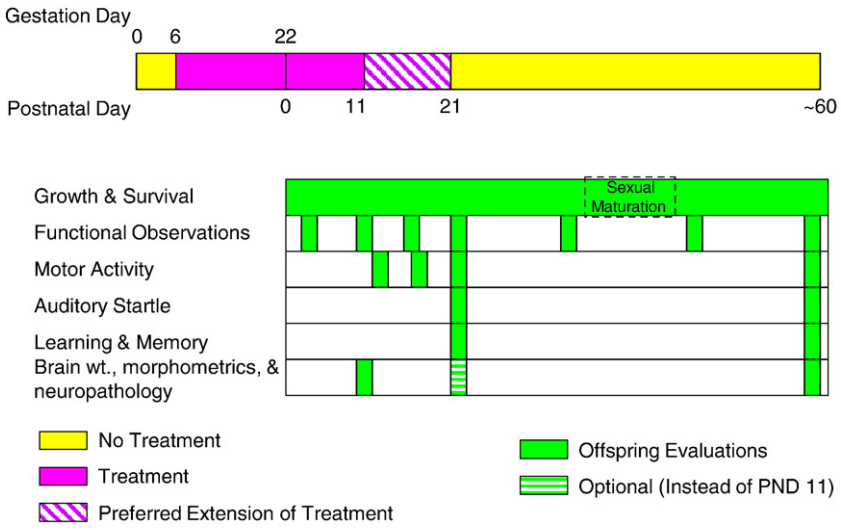

Fig. 1. DNT study design. A schematic representation of the exposure period and the parameters evaluated in the EPA guideline DNT study.

In human health risk assessments for pesticides, OPP uses animal data – including reproduction, developmental, repeated-dose and cancer studies – and appropriate human data (if available) to evaluate risks from exposure to pesticide chemicals and their metabolites in food and the environment, including the home and workplace. In spite of the increased availability of DNT data for a variety of pesticide chemicals, questions have been raised regarding the sensitivity of the current guideline study and its utility in risk assessment [7,21,31,36]. Although there are considerable data supporting the validity and sensitivity of the current EPA and OECD test guidelines [26], little information has been published regarding the use of DNT data in risk assessment. In addition, efforts are underway to develop more efficient testing paradigms for environmental chemicals, perhaps including a more limited assessment of neurodevelopmental toxicity endpoints [9]. Parallel efforts are also underway to develop more rapid and efficient screening tools that could be used to predict those chemicals likely to cause developmental neurotoxicity [8,23]. In order to provide information regarding the sensitivity and utility of the guideline DNT study and to focus future efforts, we have conducted a detailed analysis of the ways in which available DNT studies have been used in OPP risk assessments, including the frequency with which endpoints from these studies have been selected as points of departure and the types of effects that have been most frequently identified at the Lowest Observed Adverse Effect Levels (LOAELs) (preliminary analyses of these data have been presented in Raffaele et al. [33] and in Rowland et al. [34]).

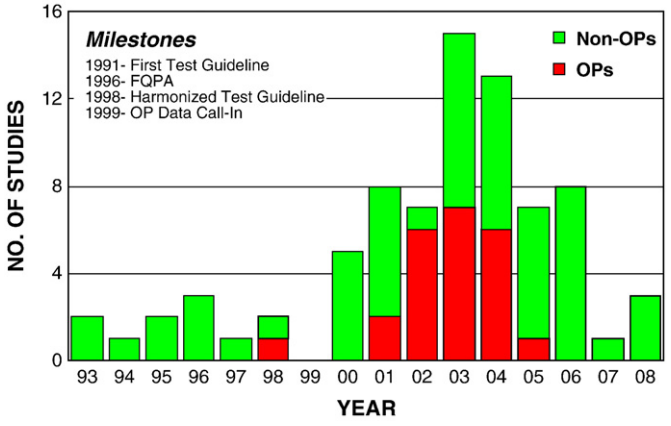

Fig. 2. DNT studies submitted to EPA/OPP, including the dates of submission. The text in the upper left corner of the figure indicates the timing of events that influenced the rate of study submission, including the finalization of the DNT guideline, passage of the Food Quality Protection Act (which required additional evaluation of risk to children), and the subsequent requirement by OPP for submission of DNT studies on additional chemicals (including a call-in for DNT studies on all organophosphate pesticides).

2. Material and methods

The analysis was conducted based on information available as of December, 2008. Information was gathered for DNT studies submitted to OPP between 1993 and 2008. All studies were submitted in support of pesticide registrations and were performed according to the EPA DNT Test Guideline (OPPTS 870.6300) [38], except that some also included slight modifications to comply with OPP recommendations for the organophosphate pesticide Data Call-In [39]. These modifications included extending the dosing period (from PND 11 to PND 21), ensuring adequate exposure to offspring (through direct offspring dosing for some chemicals), increasing the number of animals evaluated for neuropathology, and evaluating neuropathology at PND 21 instead of PND 11. Importantly, all of these modifications are consistent with the recently finalized OECD DNT Test Guideline [29].

The DNT study design that was used for the studies submitted to OPP is provided schematically in Fig. 1. Briefly, dams and/or offspring were exposed to the test substance during gestation and lactation. Both behavioral and neuropathological parameters were evaluated in offspring at early (during or immediately following lactation) and late (around PND 60) time points. Parameters evaluated in offspring included clinical signs, functional observations, motor activity, auditory startle habituation, learning and memory, and both qualitative and quantitative neuropathology. Evaluations of dams were much more limited, including only clinical observations and body weight in most studies. For some cholinesterase-inhibiting chemicals, evaluations of cholinesterase activity were also conducted for dams and/or offspring [24].

Upon submission to OPP, study reports (which include all raw laboratory data) were reviewed by EPA toxicologists to determine treatment-related effects in dams and pups at all dose levels. Detailed study reviews (Data Evaluation Reviews, or DERs) were prepared by toxicologists in the Health Effects Division (HED), OPP, and were peer-reviewed by an HED peer review committee. All final OPP DNT study reviews available as of December 2008 were identified. For each available study review, the following information was tabulated: (1) no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for offspring and maternal animals;