PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

PETA

PCRM PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

PETITION TO COMPEL THE U.S. EPA TO REPEAL ITS TEST GUIDELINES FOR DEVELOPMENTAL NEUROTOXICITY

September 30, 2004

SUBMITTED TO

The U.S. Environmental Protection Agency

SUBMITTED BY

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VIA COURIER

The Honorable Michael Leavitt
Administrator
U.S. Environmental Protection Agency
Ariel Rios Bldg. (1101A)
1200 Pennsylvania Ave. N.W.
Washington, DC 20460

RE: PETITION FOR REPEAL OF DNT TEST GUIDELINES

Dear Administrator Leavitt:

People for the Ethical Treatment of Animals (PETA), with a membership of over 800,000 supporters, and the Physicians Committee for Responsible Medicine (PCRM), representing more than 5,000 physician and 150,000 lay members, hereby call upon the U.S. Environmental Protection Agency (EPA) to repeal its test guidelines for "developmental neurotoxicity," hereinafter referred to as the "DNT," in favor of full application of the statutory tenfold (10X) safety factor provided for under the Food Quality Protection Act (FQPA) for the protection of infants and children. This petition is supported by a coalition of national animal protection and environmental organizations with a combined membership of more than 10 million Americans.

STATUTORY AUTHORITY

We submit this petition for rulemaking under the Administrative Procedure Act (APA), 5 *U.S.C.* §553(e), and its corollary in the citizens' petition provision of the Toxic Substances Control Act (TSCA), 15 *U.S.C.* §2620. A petition for rulemaking under the APA encompasses not only an application for a new rule, but the repeal or modification of an existing rule.

Subsection 553(e) of the APA requires that "[e]ach agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule." Likewise, §2620(a) of TSCA provides that "[a]ny person may petition the Administrator to initiate a proceeding for the issuance, amendment, or repeal of a rule under §2603 (chemical testing), §2605 (regulation of hazardous chemicals), or §2607 (reporting information) of this title or an order under §2604(e) or §2605(b)(2) of this title."

Thus, we submit this petition for the repeal of the DNT guidelines, in favor of full application of the FQPA 10X safety factor for the protection of infants and children.

TSCA AND FIFRA DNT GUIDELINES

According to the EPA's "OPPTS Harmonized Test Guidelines," the DNT is designed "to develop data on the potential functional and morphological hazards to the nervous system, which may arise in the offspring from exposure of the mother during pregnancy and lactation. … The test substance is administered to several groups of pregnant animals during gestation and early lactation, one dose level being used per group. Offspring are randomly selected from within litters for neurotoxicity evaluation. The evaluation includes observations to detect gross neurologic and behavioral abnormalities, determination of motor activity, response to auditory startle, assessment of learning, neuropathological evaluation, and brain weights."

EPA test guidelines for DNT studies have existed in draft and final form since the 1980s. A DNT protocol was developed in 1988 by what was then the EPA's Office of Toxic Substances (now the Office of Pollution Prevention and Toxics) for the assessment of specific solvent chemicals, and codified at 40 *C.F.R.* §795.250 (53 Fed. Reg. 5947, February 26 1988).

In 1991, the Agency finalized another DNT guideline, OPP 83-6 (Pesticide Assessment Guidelines, Subdivision F—Hazard Evaluation: Human and Domestic Animals, Addendum 10, EPA Report 540/09-91-123, March 1991). This protocol was revised in 1998 into its current incarnation, OPPTS Harmonized Test Guideline 870.6300, but has not been published in the Code of Federal Regulations. The following year, the EPA issued a data call-in (DCI) for organophosphate pesticides (OPs), which imposed several new requirements over and above those prescribed in published guidelines (EPA, 1999). Consequently, "anyone who plans to conduct a DNT study really must address the requirements instituted via the DCI notice for the OPs because that represents the new standard" (Sheets, 2003).

In 2000, the EPA published yet another DNT guideline, 40 *C.F.R.* §799.9630, as part of a final rule entitled "Toxic Substances Control Act Test Guidelines," 40 *C.F.R.* §799 *et seq.* According to the EPA's Federal Register notice: "Establishment of these guidelines provides a series of standardized test procedures and is necessary to ensure enforceable test standards in test rules promulgated under section 4 of TSCA" (65 Fed. Reg 78746, December 15, 2000). The notice further stated that the EPA "is publishing this action as a final rule without prior opportunity for notice and comment because the Agency believes that providing notice and an opportunity to comment is unnecessary."

In 2001, the EPA provided pesticide registrants with additional "Guidance on Cholinesterase Measures in DNT and Related Studies" (EPA, 2001), which further modifies and adds to the requirements of published DNT guidelines.

However, as discussed below, no DNT protocol, past or present, has ever been properly validated to confirm its reliability and relevance to neurodevelopmental effects in humans. Thus, the parties to this submission are petitioning for the repeal of two DNT guidelines, each of which constitutes a rule as defined by the APA, 5 *U.S.C.* §551(4):

1. The DNT guideline established pursuant to 40 *C.F.R.* §799.9630 shall be referred to as the TSCA DNT (attached as Exhibit 1). The bases for seeking the repeal of the TSCA DNT are: i) that it produces data of unproven reliability and relevance to humans, and therefore constitutes unsound science, and ii) that it was adopted without notice and comment rulemaking in violation of Section 553(b) of the APA. The petition for the repeal of the TSCA DNT is filed pursuant to 15 *U.S.C.* §2620(a), which permits any person to petition the Administrator to initiate a proceeding for the repeal of a rule. This aspect of the petition must be granted or denied within 90 days pursuant to Section 2620(b)(3) of TSCA.

2. We also petition for the repeal of the DNT guideline adopted under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), identified as OPPTS 870.6300 (hereinafter referred to as the FIFRA DNT and attached as Exhibit 2). The petition for the repeal of the FIFRA DNT is submitted pursuant to the APA, 5 *U.S.C.* §553(e) referred to above. The bases for seeking the repeal of the FIFRA DNT are: i) that it produces data of unproven reliability and relevance to humans, and therefore constitutes unsound science, and ii) that it was adopted without notice and comment rulemaking in violation of Section 553(b) of the APA. While cognizant that the APA does not impose a statutory deadline for an agency's response to a rulemaking petition, we submit that the substance of the EPA's response to this petition should be the same for both the TSCA and APA components, and therefore expect to receive the agency's response to the APA component within the same 90-day time window as specified under TSCA. Should the EPA anticipate a delay in providing this response, we request that the agency provide compelling justification for any delay, as well as a specific date by which the agency's complete response can be expected.

HISTORY OF THE DNT

The Food Quality Protection Act (FQPA), 21 *U.S.C.* §346a, *et seq.* requires that "an additional tenfold margin of safety for pesticide chemical residue and other sources of exposure should be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(c) further states: "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such a margin will be safe for infants and children." The Act goes on to define "safe" as "reasonable certainty that no harm will result from aggregate exposure."

Under this definition, a critical consideration is what constitutes "reliable data" that would allow the Administrator to lower the statutory 10X safety factor while guaranteeing the safety of infants and children. By its actions, the EPA has demonstrated its belief that laboratory studies of reproduction and development in animals—and in particular the DNT—provide data that are reliable for this purpose. Yet, as expanded upon below, the reliability and relevance of DNT studies has never been proven in relation to current, internationally agreed upon "validation" criteria. Indeed, much evidence exists that DNT studies do not produce reliable data within the meaning of the FQPA. Thus, the EPA's reliance upon results of unvalidated tests in its implementation of the FQPA in order to determine the appropriateness of the tenfold margin of safety for the pesticide chemical residue violates the Agency's statutorily imposed mandate to base such decisions upon reliable data. §408(b)(2)(c).

DATA QUALITY AND TEST METHOD VALIDATION

The Data Quality Act (DQA), 44 *U.S.C.* §3516 reflects Congress' requirement that governmental agencies ensure the "quality, objectivity, utility, and integrity of information disseminated by the agency…." The DQA's "Objectivity Standard" (OMB, 2002; EPA, 2002a, p. 15), requires the EPA to ensure that information it disseminates is "accurate, reliable, and unbiased." The EPA and most other federal agencies have established a government-wide data quality standard that requires proper validation of tests before the test results can be considered reliable: "Before a new or revised test method is used to generate information to support regulatory decisions, it must be … validated to determine its reliability and relevance for its proposed use…" (ICCVAM, 2003).

Likewise, for "Influential Scientific Information," such as data from a regulatory toxicity study, the EPA's Data Quality Guidelines require that the agency "ensure reproducibility for disseminated original and supporting data according to commonly accepted scientific, financial, or statistical methods" (EPA, 2002a, p. 47). However, the EPA cannot ensure reproducibility of original or supporting data regarding supposedly toxic effects to neurodevelopment until and unless those data have been generated by test methods that are reliable and relevant to the species of concern, and validation is necessary to ensure such relevance and reliability (ICCVAM, 2003).

The EPA's reliance on a non-validated DNT also violate the DQA's "Utility Standard," which requires that information disseminated by the EPA be useful to its intended users, including the public (OMB, 2002; EPA, 2002a, p. 15). Toxicity data are not useful when they are generated by unvalidated tests, which may be unreliable and/or irrelevant to the biological effect of interest in the species of concern.

Congress has specifically mandated, through passage of the ICCVAM Authorization Act, 42 *U.S.C.* §2851 *et seq*, that "each federal agency … shall ensure that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method." 42 *U.S.C.* §2851-4(c). "Validation" is defined by ICCVAM and its international counterparts as "the process by which the reliability and relevance of a procedure are established for a particular purpose" (ICCVAM, 2003, attached as Exhibit 3). The EPA's own Scientific Advisory Panel (SAP) has likewise emphasized, "that any new test guideline adopted by the Agency requires validation. This entails producing reproducible results among laboratories and selection of endpoints in test animals that are applicable to humans" (SAP, 1998).

The EPA has violated both the letter and the spirit of the ICCVAM Authorization Act by requiring, recommending and encouraging companies to submit data generated through the application of the non-validated DNT. Further, by using data of unproven reliability and relevance to humans as the basis for applying a "children's health" safety factor other than the statutory 10X, the EPA is also in violation of its obligations under the FQPA.

Reliability Issues

ICCVAM (2003) defines reliability as "a measure of the degree to which a test method can be performed reproducibly within and among laboratories over time." Ideally, reliability is assessed by means of a prospective validation study, in which the same standardized test method is performed in multiple laboratories to test a pre-determined series of test chemicals. Alternatively, reliability can be evaluated retrospectively, where historical data generated using a standardized method are available for a group of chemicals; however, this approach has a number of limitations and is generally less favorable than a prospective study. In either case, calculations are made regarding a test's intra- and inter-laboratory reproducibility and repeatability, and a conclusion is reached as to its overall reliability.

The DNT has not been subject to a level of scrutiny even remotely approximating that of a prospective, inter-laboratory validation study. Moreover, existing data and published assertions by EPA personnel do not inspire confidence in the reliability of data from DNT studies. Perhaps not surprisingly, a study of behavioral tests (which represent a core component of the EPA's DNT test guidelines), "found extreme variability in the results [of replicate neurobehavioral studies] obtained in different laboratories" (Claudio et al., 2000). In this study, three different laboratories conducted a battery of six neurobehavioral tests in inbred strains of (adult) mice. The results varied widely among the laboratories, in spite of rigorous controls of methodological variables,

including test apparatus, testing protocols, animal husbandry, acclimation times, order of administration of tests, etc. The results demonstrated that confounding influences in the laboratory environment produced widely different neurobehavioral outcomes (Crabbe et al., 1999).

Variability among DNT studies may be even greater than in the above example, due the high degree of "flexibility" the EPA permits in the choice of behavioral tests for learning and memory, as well as strain and species of animals used in DNT studies (Cooper Rees et al., 1990). In the words of one high-ranking EPA neurotoxicologist: "the outcome of a [DNT] study can depend on the inherent variability of a test measure" (Tilson, 2000). This was clearly demonstrated by a recent EPA retrospective analysis of "positive control" data in DNT studies (Crofton et al., 2004). The authors note that: "A necessary property of a good positive control chemical is that the effects on the endpoint of concern are well characterized and accepted by the general scientific community." Thus, positive controls in the context of DNT studies are substances that have been well established to be toxic to neurodevelopment. Significantly, however, the EPA's retrospective analysis found that "[l]ack of effect of the positive control chemical was a problem that occurred at least once in over 50% of the [16] test laboratories" (Crofton et al., 2004). This suggests that DNT results often cannot even be duplicated from one laboratory to another.

Relevance Issues

The ultimate goal of DNT testing is to predict with confidence the neurotoxic potential (or lack thereof) of a test chemical in human infants and children on the basis of extrapolation of data from laboratory experiments on animals. Thus, establishing the relevance of the DNT, or "the extent to which a test method correctly predicts or measures the biological effect of interest in humans or another species of interest" (ICCVAM, 2003), is of vital importance. However, the relevance to humans of laboratory tests on rodents and other animals is the subject of much controversy, due to the myriad of biological differences that exist between animal species, as well as methodological issues such as chemical dosing, behavioral measures, etc. (Derelanko & Hollinger, 2002, attached as Exhibit 4).

1. Species & Strain

Differences in Toxicity: One source of doubt regarding the relevance of animal-based test results to human hazard and risk assessment stems from the fact that different animal species—and even different strains within a species—can process chemicals quite differently. Inter-species differences can take many forms, including the rate and degree of chemical absorption, the manner in which it is circulated throughout the body and the organ(s) that may be targeted, the manner in which it is bio-transformed into active or inactive metabolites, and finally, the rate at which it is eliminated from the body (Stanton and Spear, 1990). For example, as cited in Claudio et al. (2000):

> [T]halidomide has been shown to cause limb malformations in the human fetus when exposed just once to the chemical at doses of 0.5-1.0 mg/kg. Rats, when given doses as high as 3500 mg/kg, show no teratogenic effects [birth defects]…. Effects from exposure to organophosphate pesticides (OPs) also vary among different species. For example, delayed neurotoxicity is observed in OP-exposed humans and chickens, but may not be observed in primates, rats, and rabbits….

The peer-reviewed toxicology literature is rife with similar examples. However, the true magnitude of species difference in terms of lack of concordance in toxic response is perhaps

best exemplified in a review by Schardein (1993), which presented the responses of up to 12 animal species to 11 groups of chemicals known to cause birth defects in humans, revealing profound disarray in the data.

Proponents of DNT testing point to the fact that every chemical known to cause developmental neurotoxicity in humans has been shown to produce similar effects in at least one other animal species (Francis et al. 1990). Not only is this not surprising (it seems logical that if enough animal species are tested with a chemical already known to be developmentally neurotoxic to humans, at least one will prove positive), but it is surely of dubious worth in a real-world regulatory context. It is imprudent to place any confidence in the ability of an animal test as being positively predictive for human neurodevelopmental toxicants simply because every agent that elicits DNT in humans does likewise in at least one other species; if only the reverse were true, then some of the unfortunate consequences of animal-to-human extrapolation experiments could have been avoided. What matters is to be able to show that a substance that exhibits DNT in animals poses a genuine threat to developing or infant humans, or that a substance that shows no signs of DNT in animals will likewise be non-neurotoxic to humans. Unfortunately, this, as we have shown, is where the animal-human extrapolation system has failed miserably.

Differences in Sensitivity: An EPA-commissioned *White Paper on Species/Strain/Stock in Endocrine Disruptor Assays* (Parker and Tyl, 2003), which compared the sensitivity of various rodent species and strains to selected chemicals across various toxicity endpoints, reported wildly conflicting findings. For example, one study examining the effects of the chemical ethinyl estradiol (EE) on uterine weight found Sprague-Dawley (SD) rats to be the most sensitive strain, while an almost identical study reported that SD rats were the least sensitive strain for the purpose of detecting the effects of EE on uterine weight. Similarly discordant findings were reported for the herbicide atrazine: SD rats were found to be both the most and the least sensitive rat strain for detecting atrazine's effects on estrous cycle/ovulation, and Fisher 344 (F344) rats were likewise found to be the most and the least sensitive strain for detecting atrazine's effects on fertility/gestational effects, depending on the source (Parker and Tyl, 2003, summary slides attached as Exhibit 5).

While the above examples are not specific to the DNT, it is likely that species differences are a serious confounding factor in these studies as well. For example, an EPA cross-species comparison study of the effects of PCBs on the developing nervous system (Tilson et al., 1990) found humans to be an order of magnitude more sensitive than monkeys and four orders of magnitude more sensitive than rodents to similar neonatal exposure levels. Moreover, EPA researchers (Goldey et al., 1994) studying the effects of the known human developmental neurotoxicant, methylmercury (MeHg) stated:

> It is troubling that existing test methods fail to readily detect CNS-specific effects of MeHg, a known human developmental neurotoxicant. It is clear that a search for more sensitive test methods or test species should continue. The current findings support the view that humans are significantly more sensitive than laboratory animals to known teratogens.

The magnitude and confounding effect of species differences in DNT studies was specifically addressed by an EPA Workshop on the Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity. Based on an examination of no-observed-adverse-effect-levels (NOAEL) obtained in DNT studies conducted in a variety of species, the workshop acknowledged that there was "a wide range of differences across species (up to a 10,000-fold difference)" (Francis et al., 1990). This workshop further concluded that, "[i]n many

cases—for example, lead, PCBs, and radiation—the proposed [DNT testing] battery probably would have underestimated human risk. This is true even when uncertainty factors are taken into account" (Stanton and Spear, 1990).

Differences in Developmental-Pattern-Dependent Exposure: In addition to species differences in toxicokinetics, the interpretation of DNT studies is confounded by the fact that animal species are born at developmentally different stages and mature at markedly different rates (Miller, 2003). The National Research Council (NRC) examined this issue in its 1993 report, *Pesticides in the Diets of Infants and Children*, noting: "The newborn rabbit, rat, mouse and hamster can double their birth weights in less than one week, much faster than the human infant can. These different growth velocities may alter the toxicity of pesticides and other chemicals among different species of infant animals" (NRC, 1993, p. 29). The NRC further noted that, "[t]he age period in which specific organs or tissues undergo their most rapid rate of development and the age at which development is completed have major implications for studies of toxicity to those organs in growing animals… Thus, the impact of toxic products can produce quite different outcomes that vary both with time and with species." (NRC, 1993, p. 30.)

This issue was further explored during the EPA's Workshop on the Qualitative and Quantitative Comparability of Human and Animal Developmental Neurotoxicity, which reported that, "[t]he full range of critical periods of development of nervous system in humans and experimental animals and sensitive periods of exposure to toxic agents are not well characterized" (Francis et al., 1990). This limitation raises serious doubt as to whether "windows of exposure" in the DNT are representative of all periods of neurodevelopmental vulnerability in infants and children (Claudio et al., 2000). In fact, the EPA's SAP concluded, following its review of an EPA *Retrospective Analysis of Twelve DNT Studies* (Makris et al., 1998), that: "Exposure of rat fetus/pup were not shown to be equivalent to human fetus/infant during equivalent stages of brain development, both with respect to third trimester equivalent exposure (lactational exposure in rat/transplacental in human), and in length of total exposure (does not cover extensive postnatal period of brain development in humans)" (SAP, 1999).

Rats, the recommended species in the EPA's DNT test guidelines, also differ from humans in other developmentally relevant ways. Dorman and colleagues (2001) have cautioned that "[t]here are marked interspecies differences in types of placenta, orientation of exchanging vessels, and number of exchanging layers. … [L]arge species differences have been shown for placental permeability of hydrophilic molecules. … The observed species differences in placental transfer of hydrophilic xenobiotics are caused predominantly by structural differences among placenta." Such differences may have a profound effect on the extent to which unborn rat and human fetuses are exposed to a chemical in the womb.

2. Dosing

The EPA's DNT test guidelines specify that, "the test substance…should be administered orally," which can include the addition of a test substance to an animal's diet, drinking water, or pumping it directly into an animal's stomach (known as "gavage" administration). It is well established that chemical exposure via oral gavage has the potential to deliver chemical to a target site at a rate that far exceeds anything that would occur in the real world (Conolly et al., 1999). The EPA itself (Makris et al., 1998) has acknowledged the dubious relevance of laboratory dosing procedures to realistic human exposure scenarios:

> [A]n advantage of gavage administration is that the exact measurement of the administered chemical is known and can be adjusted to body weight throughout the study. However, gavage dosing may be more irritating to the

> stomach. Additionally, gavage administration provides a discrete bolus dose of test substance while rats on a dietary study eat throughout each night and receive lower doses over multiple hours; it can be argued that neither of these scenarios is similar to human exposure to a test substance. Likewise, protocols that utilize dermal or inhalation administration (which generally expose animals to discrete 4- to 6-hour daily exposure periods that are designed to mimic worker exposure scenarios) may not have a direct corollary to human exposure in a residential setting either.

It has also been demonstrated that dosing-induced stress can produce massive damage in the liver of rats, and that prenatal stress induced by handling procedures can significantly impact the nervous system of developing pups (Claudio et al., 2000).

A further issue of concern is the EPA's specification that, "…the highest dose level should be chosen with the aim to induce some maternal toxicity (e.g., clinical signs, decreased body weight… and/or evidence of toxicity in a target organ." However, as EPA's Tilson (1992) acknowledges: "agent-induced maternal toxicity can contribute to behavioral indicators of neurotoxicity in the offspring, confounding interpretation of the data." More specifically, in the words of the EPA's *Retrospective Analysis of Twelve DNT Studies* (Makris et al., 1998):

> When developmental neurotoxicity is observed in the presence of maternal toxicity, it is often difficult to determine if the findings in young pups are secondary to the maternal toxicity. For example, decreased pup survival during early lactation and/or perinatal alterations in behavioral findings may be related to other events in either the offspring or the dam, such as an increase in the amount of the test substance in the milk at a critical time of development, inability of the offspring to suckle, general toxicity to the offspring, or insufficient maternal care of the litter.

Factors such as impaired maternal care behavior (e.g., nurturing and grooming), while critical to the growth and development of offspring, are not assessed in the DNT (Sheets, 2003). Nutrition is likewise critical to pups' growth and development, yet milk quantity and quality are not evaluated, nor are measurements recorded of components in the milk (Sheets, 2003). Maternal toxicity during the *in utero* phase may be equally problematic, as a result of reduced maternal food consumption, maternal pulmonary damage, maternal renal damage, effects on the maternal central nervous system, etc. (Tyl and Sette, 1990). Thus, "under circumstances of severe toxicity, you cannot distinguish whether effects are due to developmental neurotoxicity or secondary to maternal toxicity" (Sheets, 2003).

Because developing animals are exposed to a test substance via the dam—which relies on transport of the substance through the placenta or via lactation—the actual level(s) and route(s) of exposure levels in the pups are highly speculative (Claudio et al., 2000; Dorman et al., 2001). The EPA's Makris and colleagues (1998) clearly acknowledge this problem, noting:

> For developmental neurotoxicity studies reviewed by the Agency, there is generally a lack of knowledge regarding actual exposure of the chemical to the offspring *in utero* or via the milk. Pharmacokinetic data, which might assist in this determination, are not addressed in the standard developmental neurotoxicity study guideline… This suggests that a developmental neurotoxicity protocol which includes direct postnatal exposure may be necessary to adequately evaluate the developmental neurotoxic potential of some chemicals… although

> no standardized testing guideline for postnatal dosing has been developed by the Agency.…

This finding was echoed by the Agency's Risk Assessment Forum, which noted: "Under the DNT protocol, there is currently no requirement to perform kinetic studies to ascertain either *in utero* or postnatal exposure. There is no mechanism to guarantee exposure postnatally (i.e., direct dosing of pups) because the compound may not be excreted into breast milk or it may be excreted only at very low concentrations" (RfD/RfC Panel, 2002).

Direct dosing of pups has been proposed as a means of resolving questions surrounding route of exposure, dose levels, etc. However, according to Miller (2003) of the Centers for Disease Control: "Direct dosing requires a lot of manipulation of the animals [and] is itself a problem. The continued handling of pups required in direct dosing can affect the endpoints of the developmental neurotoxicity study, especially the behavioral endpoints that are being evaluated at the same time." The unavoidable stress and potential injury to pre-weaning pups by oral force-feeding has been documented to cause a host of non-specific functional and/or behavioral changes that have nothing to do with a chemical's toxic mode of action, thus confounding interpretation of the results of certain DNT studies (Conolly et al., 1999). Sheets (2003) has therefore questioned:

> Does this provide a relevant circumstance for use in risk assessment? I think we all agree that such a dose does not model dietary, dermal, or inhalation exposure that children may experience in the real world. … If the pesticide does not pass through the milk, then it would be inappropriate to dose pups by gavage because it would not be relevant to a human circumstance of exposure. It is important to remember that this is not a research project to satisfy scientific curiosity; this is a study that should model realistic human exposure circumstances.

3. Behavioral Measures

Behavioral testing has become a central component of DNT studies due to the perceived sensitivity of behavioral endpoints in detecting subtle chemical insults to the central nervous system. However, current measures of an animal's cognition, sensory-motor function, and other behavioral parameters are numerous and diverse, often differing widely in terms of the subjectivity of observations, breadth and specificity of results, quantity and quality of available validation data, and extrapolation of results among species (Cory-Slechta et al., 2001). For example, Elsner (1992) has commented:

> Experimental psycho-teratology, with the purpose of determining potential effects of chemical exposures during brain development on human behavior, assumes that behavior of experimental animals is a valid model for human behavior. This practice implicitly takes for granted that changes in animal behavior, which are detectable in artificial laboratory settings, relate directly to sometimes poorly understood and highly complex psychopathologies in the diversified human environment. It is understandable that this bold assumption is doubted by many neurotoxicologists…

As detailed by Anger (1990), laboratory tests employed to assess the effects of chemicals in animals "differ markedly" from those used to assess neurotoxic effects in humans. Anger's comparison of laboratory and human clinical and occupational assessment techniques "reveals a lack of parallelism between the screening tests that will be employed to test animals and

those used to assess humans, suggesting that the respective tests do not test similar functions." For example, sensory tests in human volunteers include sophisticated measures of visual perception and memory, whereas the animal-based tests for sensory function include simplistic "finger snap response," "tail pinch response," and "pupil response" (Anger, 1990). A similar picture emerges for assessments of affect, cognition, memory/learning, and psychomotor function. In the words of the head of Health Canada's Pest Management Regulatory Agency (Franklin, 1999): "Few if any standardized/validated protocols have yet been established which specifically address cognition, memory and higher brain function." Thus, "few studies of higher neurobehavioral function in humans and animals are directly comparable" (Davis et al., 1990).

Exacerbating this problem is the question of whether current behavioral measures of learning and memory can accurately be applied early in a rodent's life span, and whether they are sufficiently sensitive to detect subtle effects on the central nervous system (SAP, 1999; Claudio et al., 2000). Indeed, the agency's SAP "was divided whether the methods identified [in the EPA's DNT guidelines] are reasonable for assessment of toxicity to offspring."

Also widely recognized is the fact that reliance on often subjective behavioral observations, versus more objective physiological measures, has the potential to introduce major uncontrolled variability into conduct and interpretation of DNT studies (Claudio et al., 2000; Tilson, 1995; Gerber and O'Shaughnessy, 1986). Studies that have relied upon neurobehavioural tests have suffered from poor inter-laboratory reproducibility, even where rigorous control has been maintained over variables such as test apparatus, testing protocols, animal husbandry, acclimation times, order of administration of tests, etc. (Crabbe et al., 1999). This situation is particularly worrisome in view of the fact that EPA DNT test guidelines allow investigators considerable "flexibility" in their choice of methods of behavioral testing.

Another question relates to the specificity of behavioral tests for neurotoxicity, or their ability to distinguish between "true" neurotoxicity as distinct from more generalized systemic toxicity. This question was examined by Gerber and O'Shaughnessy (1986), who concluded:

> These results further illustrate the point that none of the standard behavioral tests are unique indicators of impaired central nervous system function. All the behavioral tests used in this study were affected by impairment of critical systemic organs as well as by restriction of food and water intake. Before it can be concluded that a compound is neurotoxic on the basis of behavioral test results, it must be ascertained that non-neural organs have not been damaged by the test compound, and that food and water consumption have not been severely decreased. Unless these factors are considered, it is possible to obtain a behavioral test result that suggests a neurotoxic effect, but which is actually the consequence of systemic organ toxicity.

Thus, experimental behavioral endpoints may only be detecting the fact that an animal is experiencing a pharmacologic central nervous system effect that is transient and not related to a true neurotoxic effect. For example, alcohol could be expected to alter an individual's response to a behavioral test at doses well below those that might be associated with neurotoxicity.

In an attempt to overcome some of these well-known and serious limitations, the EPA turned to the International Life Sciences Institute (ILSI) for assistance. ILSI's Risk Science Institute responded by convening a working group of experts from government, industry, academia and the public interest sector to review these issues (Mileson and Ferenc, 2001). The report of the ILSI working group on behavioral effects was particularly enlightening, noting, among other things, that "…there are numerous examples of the misuse of these methods and misinterpretation of

results derived from these methods" (Cory-Slechta et al., 2001, attached as Exhibit 6). For example:

- *Hindlimb Splay Test:* "[D]espite its popularity and its inclusion in the US EPA neurotoxicity testing guidelines, little is known about this test. The anatomic basis for the test is unknown, there is no obvious analog used by veterinary or human neurologists, and the neurologic basis for the test can only be hypothesized. The rationale for using the width of the response as an index of function is not at all clear."
- "Behavioral tests of sensory endpoints are sensitive to a wide variety of environmental variables (e.g., ambient noise, handling history, time of day)…"

- "A current dilemma in assessing motor function is that tests of reflexes and reactions are relatively quick and easy to perform, but their sensitivity in the context of DNT testing is uncertain. … There is a need to develop and validate technology and procedures that measure motor function objectively and sensitively, yet are sufficiently flexible to be used with large numbers of animals."

- "Interpretation of motor function tests must take into account the limitations of the test equipment as well as any potential biological confounders."

- "[S]imple approaches to measurement of memory such as the frequently employed passive avoidance paradigm also present difficulties of interpretation."

- "Some endpoints are recorded subjectively, using categorical (present/absent) or ordinal (e.g., absent, minimal, moderate, severe) scales. For these endpoints, the data are based upon the judgment of the tester…"

- "Few reports include measures of inter-observer reliability or training procedures. Agreement among laboratories must be achieved if social behaviors are to serve as useful endpoints. … It would be rare for a group of experts in maternal behavior, for example, to agree on common definitions and approaches so that data from different laboratories can be compared. … Automation is not yet a common feature of social behavior research. … Little standardization has been accomplished…"

4. Structural (Neuropathology) Measures

Jensen and Catalano (1998) acknowledge that there is currently a "… limited understanding of the morphological basis of developmental neurobehavioral disorders. Our ignorance is exemplified at one extreme by debilitating disorders that do not appear to be associated with any detectable morphologic defect. At another extreme is the occurrence of dramatic congenital alterations in the brains of individuals that exhibit only minimal, if any, functional impairments." It should therefore come as no surprise that the ILSI working group on neuropathology assessment (Garman et al., 2001, attached as Exhibit 7) identified a litany of potential confounding factors and other limitations associated with DNT studies. For example:

- "… regressive events essential to normal development such as programmed cell death must be distinguished from treatment-related effects that may exhibit similar morphologic characteristics" lest they be misconstrued as pathologic.

- "Various guidelines may require the examination of brains from postnatal day (PND) 11 or PND22 rats, as well as the brains of young adult rats (usually PND60). Note that methods of classifying rat ages vary from laboratory to laboratory. The first 24 hr after pairing of the adult male and female rat may be classified as embryonic day (E) 0, or E1, depending on the laboratory. Similarly, the day of birth may be considered PND0 or PND1."

- "PND11 rat brains have high water content and are nonmyelinated. Therefore, they are very soft and easily traumatized. Some anatomic structures that might be used as gross dissection guidelines, such as the optic chiasm, are difficult to visualize at this young age. The cerebellum of PND11 brains is incompletely formed, making it difficult to achieve highly standardized coronal sections of this structure."

- "Brains of juvenile rats may be placed in Bouin's fixative to enhance their firmmess, although fixation in Bouin's will cause brain shrinkage and should be controlled carefully. For example, experience (in the first author's laboratory) using Bouin's fixative after formalin fixation caused approximately 23% decrease in brain weight and 7% decrease in anterior-to-posterior brain length measurement for PND12 rats."

Among the conclusions of the ILSI neuropathology working group was that: "Differences between species in the rates and complexities of biologic processes underlying neurologic development contribute significantly to the challenge of using animal species, such as the rat, to predict the neurotoxic potential of a chemical in humans" (Garman et al., 2001).

Summary of Data Quality & Validation Issues

The DNT's lack of validation—and therefore dubious reliability and relevance to humans—has been clearly recognized by experts in the fields of test method validation, toxicology, and pediatric medicine (see affidavits from the past head of the European Centre for the Validation of Alternative Methods, Prof. Michael Balls; former EPA toxicologist Dr. Chad Sandusky; pediatrician Dr. Suzanne Morris; neurobiologist Dr. Gill Langley; and former government industrial hygienist Jessica Sandler). The EPA itself has acknowledged the litany of problems associated with the conduct and interpretation of DNT studies, which was summarized by Makris and colleagues (1998) as follows:

> It is recognized that the conclusions drawn from this initial retrospective survey of developmental neurotoxicity data must be examined in light of the many confounding factors that may have contributed to the study results and conclusions. Some of these factors are common to many or all of the studies, such as the influence of dose selection on determination of the NOEL [no-observed-effect-level], inaccuracies or inconsistencies in the conversion of dietary or inhalation dose levels to mg/kg/day values, a lack of knowledge regarding actual exposure of the chemical to offspring *in utero* or via the milk (pharmacokinetic data), or differences in the endpoints examined for the various protocols (for example, the timing of measurements, variations in laboratory procedures, missing or inadequate assessments of any particular endpoint). Some factors are specific to a chemical or a particular study protocol. These might include utilization of knowledge on the chemical to aid in the selection of tests to assess learning and memory or of the most appropriate species for testing. It is also acknowledged that the conclusions of the studies, as well as the

> endpoints selected for risk assessment, are often issues of contention between the Agency and the regulated community. There are ongoing, unresolved controversies regarding some of the studies presented in this paper as well as some of the Agency decisions cited in this analysis.

In the absence of proper validation, EPA cannot conclude that the results of DNT studies have any bearing on the potential threat of the investigated substance to humans, particularly infants and children. This conclusion was also expressed by a panel of the National Academy of Sciences, which reported: "the subcommittee finds that the developmental neurotoxicity test, as it is currently described in the U.S. Environmental Protection Agency (EPA) guidelines (EPA 1991), might be inadequate to identify and characterize specific developmental neurotoxicants (CLS, 2000). Similarly, in the words of one EPA scientist (Rice et al., 1996):

> It is clear from comparison of the human and rodent data that the results from rodent studies often vastly underestimate intakes at which neurotoxicity was observed in humans. For lead, deficits were revealed on activity and simple learning tests at doses that would also result in allowable intakes much higher than those at which cognitive impairment has been demonstrated for children. One conclusion that may be drawn from this analysis is that current methods of calculating acceptable intakes based on animal data … are insufficient to protect the human population against behavioral toxicity.

Likewise, when asked by the EPA for its opinion as to the sensitivity of the DNT relative to other developmental or reproductive toxicity studies, the SAP stated: "The DNT is not more sensitive in its current form, given what is known in the broader neuroscience and pediatric community… Therefore, the current form of the DNT guidelines … is not a sensitive indicator of toxicity to the offspring" (SAP, 1999).

EPA VIOLATED THE APA BY FAILING TO PROMULGATE THE FIFRA DNT AS A RULE AND BY PROMULGATING THE TSCA DNT AS A FINAL RULE WITHOUT PUBLIC NOTICE AND AN OPPORTUNITY FOR PUBLIC COMMENT

Notice of availability of the FIFRA DNT and approximately 60 other draft OPPTS test guidelines was published in the Federal Register on June 20, 1996, and interested persons were invited to submit written comments (61 Fed. Reg. 31522). More than two years later, on August 5, 1998, the EPA published notice of availability of final test guidelines, which included the FIFRA DNT (63 Fed. Reg. 41845). However, this guideline was never promulgated as a rule or published in the Code of Federal Regulations.

Nonetheless, the EPA has on multiple occasions required pesticide registrants to conduct DNT studies, both through a 1999 data call-in (DCI) initiative (a summary of which are attached as Exhibit 8) and as a condition of registration under FIFRA §3(c)(7)(B) and §3(c)(7)(C) (summaries of which are attached as Exhibit 9). The Agency's long-standing circumvention of formal rulemaking procedures (i.e., through the amendment of its pesticide registration data requirements as codified under 40 *C.F.R.* §158.340 and §158.490) represents a glaring and chronic violation of the APA's notice and comment rulemaking requirements. Moreover, the EPA's 1999 DCI notice for organophosphate pesticides (OPs) imposed several new requirements over and above those required pursuant to FIFRA DNT (see also EPA, 2002c). Consequently, "anyone who plans to conduct a DNT study really must address the requirements instituted via the DCI notice for the OPs because that represents the new standard" (Sheets, 2003). Subsequent to the 1999 DCI, EPA provided pesticide registrants in October 2001 with

supplemental "Guidance on Cholinesterase Measures in DNT and Related Studies" (EPA, 2001), which further modifies and adds to the requirements of the FIFRA DNT.

It is widely recognized that the Agency intentionally and systematically uses "guidelines" and "guidance documents" as a means to avoid notice and comment rulemaking. The Agency's penchant for promulgating guidelines and guidances instead of observing the notice and comment rulemaking requirements of the APA, has not gone unnoticed by the judiciary. In the case of *Appalachian Power Co. v. EPA*, 208 F.3d 1015 (D.C. Cir. 2000), the Court chastised the EPA for issuing guidance documents as a subterfuge aimed at evading both notice and comment rulemaking and judicial review. As the Court observed:

> The phenomenon we see in this case is familiar. Congress passes a broadly worded statute. The agency follows with regulations containing broad language, open-ended phrases, ambiguous standards and the like. Then as years pass, the agency issues circulars or guidance or memoranda, explaining, interpreting, defining and often expanding the commands in the regulations. One guidance document may yield another and then another and so on. Several words in a regulation may spawn hundreds of pages of text as the agency offers more and more detail regarding what its regulations demand of regulated entities. Law is made, without notice and comment, without public participation, and without publication in the Federal Register or the Code of Federal Regulations.

Id. at 1020. The Court in *Appalachia Power* went on to hold that the document at issue, the Periodic Monitoring Guidance, was in fact a final rule promulgated in violation of the notice and comment rulemaking provisions of the APA. As a consequence, the Court threw out the guidance in its entirety.[1]

Other cases in the District of Columbia Circuit reflect similar rulings. For example, in *Mobil Oil Corp. v. EPA*, 35 F.3d 579 (D.C. Cir. 1994), the Court declared that EPA's repromulgation of a portion of a previously vacated interim rule without notice and comment rulemaking, was procedurally defective and therefore invalid. In *State of New Jersey Department of Environmental Protection v. EPA*, 626 F.2d 1038 (D.C. Cir. 1980), the Court held that exceptions to notice and comment rulemaking strictures are narrowly construed and accordingly, set aside the challenged rule. The Court in *Wagner Electric Corp. v. Volpe*, 466 F.2d 1013 (3d Cir. 1972), cautioned the Agency that the petition for repeal of a rule is no substitute for proper notice and comment rulemaking in the first place. And most recently, in *General Electric Company v. EPA*, 290 F.3d 377 (D.C. Cir. 2002), the Court held that an EPA guidance document relating to PCB clean-up plans was a rule subject to the APA, and since it was not promulgated pursuant to notice and comment rulemaking, the guidance was vacated.

In 2000, the EPA published the TSCA DNT (i.e., 40 *C.F.R.* §799.9630), as part of a final rule entitled "Toxic Substances Control Act Test Guidelines." According to the EPA's Federal Register notice: "Establishment of these guidelines provides a series of standardized test procedures and is necessary to ensure enforceable test standards in test rules promulgated under section 4 of TSCA" (65 Fed. Reg 78746, December 15, 2000). The notice further states that the EPA "is publishing this action as a final rule without prior opportunity for notice and comment because the Agency believes that providing notice and an opportunity to comment is unnecessary." This action by the Agency represents yet another glaring violation of the APA, which requires that

[1] The *Bureau of National Affairs* published a Special Report article on the holding in the case. The author's opening salvo charges the EPA with "a special fondness for issuing 'guidance documents' thereby avoiding the rulemaking process" (Stoll, 2000, attached as Exhibit 10).

agencies give interested persons an opportunity to participate in rule making through submission of written data, views, or arguments (see 5 *U.S.C.* §553(c)).

In view of the foregoing, we seek the repeal of the FIFRA and TSCA DNT guidelines because they have been promulgated in non-compliance with the APA.

PUBLIC POLICY CONSIDERATIONS

There are several additional points we ask the Administrator to consider in conjunction with the lack of scientific validation the DNT and the agency's failure to observe notice and comment rulemaking procedures. Those are the public policy considerations expressed in the ICCVAM Authorization Act, the National Institutes of Health Revitalization Act of 1993 (42 *U.S.C.A.* §283e), the FQPA, and the DQA. These Acts express, respectively, Congressional intent regarding the validation of toxicity test methods, and the reduction, refinement, and ultimate replacement of animal use in toxicity testing, the precautionary regulation of pesticides and other chemicals, and the soundness and integrity of information disseminated and used by federal agencies. Each Act positively supports the merits of this petition.

One of the central aims of the ICCVAM Authorization Act is to promote and advance alternatives to animal-based testing. In establishing the ICCVAM as a permanent Committee, Congress signaled its firm commitment to the advancement of *in vitro* and other non-animal-based testing methods. ICCVAM's mandate is clear: new and revised test methods are to be scientifically validated and reliance on animal-based methods must be reduced, refined and replaced. At least 1,300 animals are killed for every DNT "guideline study" that is performed—although for practical purposes, "anyone who plans to conduct a DNT study really must address the requirements instituted via the DCI notice for OP's because that represents the new standard" (Sheets, 2003). This revised study design may kill as many as 2,600 animals (Mattsson et al., 2003) at a cost of up to $1 million per active ingredient (Werner, 2000). Moreover, to the extent the DNT has been revised, it was done so without being validated as called for in the statute. The DNT is an affront to ICCVAM's mandate.

The NIH Revitalization Act of 1993 directs the National Institutes of Health, through an Interagency Coordinating Committee on the Use of Animals in Research, to prepare a plan to conduct or support research into methods of research that "do not require the use of animals," that "reduce the number of animals used in such research," that encourage the "acceptance by the scientific community" of alternative methods, and that trains "scientists in the use of such methods." 42 *U.S.C.* §283e. It is clear from the language of the statute that Congress intended for the EPA to be an active contributor to development and implementation of the above-mentioned plan, as involvement by "representatives of the Environmental Protection Agency…" on the interagency committee is a specific requirement under the Act.

The FQPA and the DQA, discussed above, promote application of the precautionary principle and the quality, objectivity, utility, and integrity of information disseminated by the agency. The DNT guidelines stand in stark contrast to the letter and spirit of both Acts.

From a public and children's health perspective, it is clear that given the uncertainties and subjectivity associated with the DNT, this test method cannot serve to guarantee that infants and children are safe and adequately protected from adverse effects associated with pesticide or other chemical exposures (HIARC, 1998; HIARC/FQPA-SFC, 1998). In public comments presented in 1999, the now senior director of the American Chemistry Council's Public Health Team stated, in reference to the findings of Makris et al. (1998):

> The DNT studies had little or no impact on regulatory risk assessment. For 8 of 12 substances, maternal toxicity was shown to occur at the same or lower dose than adverse effects in offspring. Of the remaining 4 studies, 2 chemicals were associated with decreased pup body in developmental toxicity studies—effects which can be seen in reproduction or developmental toxicity studies. Therefore, the Makris et al. review actually shows that either maternal toxicity or developmental toxicity commonly occurs at comparable or lower dose levels than developmental neurotoxicity. Based upon the available studies, the DNT data do not appear to afford additional or increased level of public protection over that afforded by assessing risks from reproduction, developmental or other toxicity studies.

To date, DNT data have not been used as the basis for setting even a single chronic dietary reference dose (RfD) (Makris et al., 1998), which means "there were other studies that were more sensitive than the NOELs [no-observed-effect-levels] generated from the DNT. For acute RfD, the DNT study was used three times. In two of these cases, the RfDs were based on maternal toxicity, not pup toxicity. One acute RfD was based on pup toxicity. In evaluating this one acute RfD, there were also NOELs from other reproduction/developmental studies that were really hovering right around that same NOEL as the DNT study, if not lower like the two gen repro study" (Li, 2003).

Nor has the DNT lead to the lowering of any pre-existing reference doses for pesticides. In fact, quite the opposite situation has emerged. In its revised assessment of the cumulative risks of organophosphate pesticides, the EPA actually removed the statutory FQPA 10X "children's health" safety factor for 30 such substances, replacing it with factors of 1X and 3X, respectively (EPA, 2002b). As stated by the American Industrial Health Council (AIHC, 1999):

> EPA ignores the key outcome [of the *Retrospective Analysis* by Makris et al. (1998)] that the developmental neurotoxicity tests have not caused a single chemical on the list of 12 to be regulated at lower exposure levels than the levels that can be determined by other more traditional toxicology tests…. EPA's level of confidence in the ability of extensive developmental neurotoxicity testing to lead to greater protection of children's health is simply overstated and unsupported by the evidence.

Remarkably, the EPA has even required DNT studies in cases where the Agency itself admits to knowing beforehand that there would be no value added. A telling example can be found in a November 6, 2002, letter from then EPA Pesticide Chief, Marcia Mulkey, to the heads of the American Farm Bureau Federation and CropLife America:

> The recent tolerance action for lambda-cyhalothrin is an example of a situation where a new study, a developmental neurotoxicity study, has been required but not yet submitted; however, OPP was able to conclude "that existing, reliable toxicity data provide reasonable certainty that a risk assessment conducted using no additional factor (1X) will protect the safety of infants and children." 67 FR 60902, 60911 (Sept. 27, 2002). In reaching this decision, OPP considered a number of factors bearing on what effects the developmental neurotoxicity study might show and at what dose level those effects might occur. Id.; accord 67 FR 60950, 60955 (finding no additional safety factor necessary for triticonazole despite lack of developmental neurotoxicity (DNT) study because the "DNT is unlikely to affect the manner in which triticonazole is regulated.")

Consultants in Toxicology, Risk Assessment and Product Safety similarly concluded that, "This thrust of EPA's policy development contradicts both statutory language and Congressional intent. … [T]he Agency has set off on a tangent of creating new, unvalidated toxicology tests, to test pediatric endpoints. This process is hopeless. The science of toxicology is such that animal tests will always produce false positive and false negative predictions of human health effects" (Byrd, 1999).

The Administrator would better serve the public and children's health—as well as the EPA's various statutory obligations, described above, to base its regulatory decisions on sound science developed using validated test methods—by presumptively applying the FQPA-mandated 10X factor using currently available information. Presumptive application of the 10X safety factor would also be consistent with recommendations by environmental and children's advocacy groups, including the Natural Resources Defense Council (Wallinga, 1998), which has concluded that:

> [F]or certain data gaps for children's exposure and toxicity, the agency generally has more than enough data for many pesticides … to necessitate immediate serious reductions in, or revocations of, their tolerances. Thus, there is absolutely no reason for EPA to wait to make these decisions. Strong and immediate presumptive use of this tenfold safety factor is necessary not only to protect infants and children, but also to ensure that ten years from now we are not still waiting for data to show, with reasonable certainty, that pesticides pose no harm to our children.

For the foregoing reasons, we respectfully urge the Administrator to repeal the EPA's DNT test guidelines in favor of full application of the FQPA 10X safety factor for the protection of infants and children.

Respectfully submitted,

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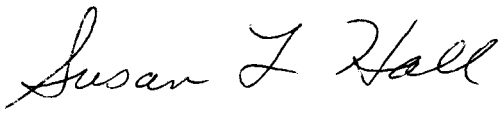

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