September 7, 2005

These comments are presented to the EPA in response to the following notice and request for comments:

ENVIRONMENTAL PROTECTION AGENCY [OPPT–2004–0387; FRL–6811–2]
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Re: EPA 40 CFR Parts 152 and 158 pesticides; Data requirement for Conventional Chemicals; Proposed Rule

Docket ID No. OPP-2004-0387

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These comments are respectfully submitted by:

- The Natural Resources Defense Council (NRDC)
- Pesticide Action Network, North America (PANNA)
- Northwest Coalition for Alternatives to Pesticides (NCAP)
- The Endocrine Disruptor Exchange (TEDX)
- American Bird Conservancy (ABC)
- Farmworker Justice Fund
- Beyond Pesticides/NCAMP
- Alaska Community Action on Toxics (ACAT)

We are non-profit advocacy groups with a shared goal of protecting human and ecological health through the use of law, science, and the support of more than 1 million members and supporters. We support the EPA Administrator and the Office of Prevention, Pesticides and Toxic Substances (OPPTS) in its stated goal to, "*regulate pesticides and chemicals to ensure protection of public health and the environment, as well as promote innovative programs to prevent pollution*".[1]

GENERAL COMMENTS:

Intentional exposure/dosing studies on infants, children, young adults, or any other sensitive population are unethical and unscientific

We support the collection of human exposure data. However, we are very disturbed at suggestions that the Agency may expand its testing requirements to include human exposure data from intentional dosing regimes. The FR notice states that the requirements of the FQPA to reassess all pesticides with special consideration of the "potential pesticide risk to children" may, "necessitate collection of additional data on drinking water and non-occupational and residential exposures." (FR, p. 12280). The FR notice points out that, "the Agency believes it should detail more specifically the conditions under which these tests will be required." (FR, p. 12280). In its discussion of post-application exposure data requirements, the Agency states that "in some instances…EPA may require a biological monitoring study." (FR, p. 12300). Such data needs should never be used to authorize an intentional exposure/dosing study on infants, children, young adults, or any other sensitive population. We encourage EPA to adopt binding rules that regulate all human tests and include all of the protections recommended or required by the National Academy of Sciences, the EPA Scientific Advisory Panel and Science Advisory Board, the international Helsinki Declaration, the Nuremberg Code, and applicable U.S. laws and regulations.

We Support the Refinement and Consolidation of Testing Regimes

Without adequate laboratory testing, the default method for identifying human hazards is epidemiology. This is, unfortunately, neither rapid nor protective. We strongly support the combined study protocol proposed by EPA, the refinement of tests, and the replacement of animal tests with validated non-animal tests as they become available. Such refined and combined study protocols are expected to reduce replication of studies, reduce the number of animals to be sacrificed, and most important, introduce the concept of concomitant damage across a number of systems (FR, p. 12296). As EPA begins to look "holistically" at the damage in an animal it will begin to produce data that better explains the manifestation of disease. Using this approach a very realistic picture of the damage caused by a pesticide will be available which should match better what is happening in humans. Ultimately in the end, more causal relationships are likely to be revealed. An example of such a testing scenario proposed in the revisions to Part 158 would be the use of a comprehensive screen of functional and structural thyroid perturbation (i.e., including T3, T4, and TSH levels) in adult and young animals. Another example is the suggestion that developmental neurotoxicity studies be conducted in combination with a two-generation reproduction study, in addition to the evaluation of structural or functional toxicity of other organ systems in immature animals (FR, p. 12296).

The animal bioassay is an accepted testing method because the vast majority of human carcinogens have also been shown to be carcinogenic in animals[2], and many chemicals first identified as carcinogenic in animals were subsequently confirmed to be human carcinogens as well.[3] Well-designed animal studies provide detailed dose-exposure information, repeatability, sufficient statistical power, and comprehensive behavior and histopathological information.[4] We support the efforts by EPA and the scientific community to develop validated non-animal tests, and encourage the appropriate integration of data from validated 'omics and in vitro toxicity testing methods. However, we are years, if not decades, from fully understanding the cellular and subcellular mechanisms of carcinogenicity, and therefore suggest that an appropriate goal at this time be to further characterize cellular and subcellular toxicity, in order to refine our understanding of chemicals and toxic agents on health and disease. Mechanistic-based endpoints derived from both animal and non-animal tests will be most useful if comparative data can be developed in both humans (passive dosimetry and epidemiology) and animal models. We encourage the development of biologically based dose-response models that can be used for trans-species extrapolations of toxic or carcinogenic effects, and that can address inter-individual differences in susceptibility as well as the effects of exposures to mixtures. Such data will help to refine and consolidate current testing methods. The validation and appropriate integration of microarray and 'omics technology will require a clear strategy, to contribute to the design or interpretation of toxicity testing. As the scientific community identifies critical mechanistic endpoints in the progression of disease, EPA should consider incorporating these into low-dose testing regimes, and observe for appropriately sensitive endpoints.

Suggested improvements for test protocols

EPA should turn to the open literature for guidance when selecting the new endpoints for evaluation in the combined assays. More functional and histological endpoints need to be incorporated. It is unacceptably limiting for EPA

to depend only on guideline study results to develop new endpoints, while ignoring or only giving cursory attention to the work of academic laboratories and field studies that in some cases have spent more than a decade examining the health and ecological impacts of pesticides. For example, there is a plethora of published data reporting on neurodevelopmental impacts of the organophosphate pesticides on the brain, CNS, and peripheral nervous system.[5] Thorough, in-depth testing should be required of all pesticides regardless of class. Recent discoveries about pesticides, from insecticides to herbicides and fungicides, that interfere with catecholamines reinforces this need.[6] The Agency should no longer be able to subjectively remove a pesticide from a series of tests.

There is an immediate need to incorporate testing at ecologically relevant doses, particularly for hormone disrupting chemicals for which non-linear and/or inverse dose response relationships are likely to exist.

We support the addition of functional and/or behavioral effects in the acute and subchronic battery of neurotoxicity studies (FR, p. 12294). These are critical improvements and will generate important data to aid the Agency in its evaluation of neurotoxic and teratogenic chemicals.

We support the inclusion of tests that include end-use products (EP), as well as the technical grade active ingredient (TGAI), and encourage the Agency to also include tests of mixtures of chemicals that are commonly used together, and for which common exposures are likely (FR, p. 12296). Additionally, testing of inert ingredients alone and in formulations will also provide critical information for realistic assessments. We encourage the Agency to collect these data, and suggest that it is critical for evaluating any additive or synergistic effects, and real-world exposure scenarios.

SUMMARY OF CURRENT CORE TESTS:

Currently required tests for non-food use pesticides include:

- Acute toxicity set (six tests): oral, dermal, and inhalation toxicity; plus primary eye irritation, skin irritation, and skin sensitization.
- Mutagenicity battery: tests of gene mutation, structural chromosomal aberrations, and genotoxic effects

Required for food use pesticides:

- Acute toxicity and mutagenicity tests, as above, plus,
- Subchronic (90-day) feeding study, typically rat and dog
- Chronic (2-year) combined feeding study/carcinogenicity study in two species
- General metabolism study, in rats
- Developmental toxicity study, typically rabbits and rats
- Reproductive, or two-generation study, typically rats

Additional tests:

- Acute delayed neurotoxicity: hen (only required for organophosphate pesticides)
- Developmental neurotoxicity study in rats (as needed)

COMMENTS ON CURRENT AND PROPOSED CORE TOXICITY TESTS (FR, p. 12292-12298):

Acute				
Current requirement	*Guideline*	*Proposed requirement*	*Change*	*Comment*
Acute oral toxicity - rat	870.1100	Acute oral toxicity - rat	Modified test substance to read, "TGAI, EP and possibly diluted EP" for an end-use	We support inclusion of studies using the end-use product (EP), to provide useful data. We encourage the substitution of the acute toxicity battery of tests with NICEATM[7]-validated non-animal and in vitro tests as they become available.

			product	
Acute dermal toxicity	870.1200	Acute dermal toxicity	Modified test substance to read, "TGAI, EP and possibly diluted EP" for an end-use product	We support inclusion of studies using the end-use product (EP), to provide useful data. We encourage the substitution of the acute toxicity battery of tests with NICEATM-validated non-animal and in vitro tests as they become available.
Acute inhalation toxicity - rat	870.1300	Acute inhalation toxicity - rat	No change	We encourage the substitution of the acute toxicity battery of tests with NICEATM-validated non-animal and in vitro tests as they become available. We urge EPA to require inhalation toxicity studies for all pesticides with vapor pressures greater than 10^{-5} mm Hg.
Primary eye irritation - rabbit	870.2400	Primary eye irritation -rabbit	Added testing using TGAI to support end-use products	We support inclusion of studies using the end-use product (EP), to provide useful data. We encourage the substitution of the acute toxicity battery of tests with NICEATM-validated non-animal and in vitro tests as they become available.
Primary dermal irritation	870.2500	Primary dermal irritation	Added testing using TGAI to support end-use products	We support inclusion of studies using the end-use product (EP), to provide useful data. We encourage the substitution of the acute toxicity battery of tests with NICEATM-validated non-animal and in vitro tests as they become available.
Dermal sensitization	870.2600	Dermal sensitization	Added testing using TGAI to support end-use products	We support inclusion of studies using the end-use product (EP), to provide useful data. We encourage the substitution of the acute toxicity battery of tests with NICEATM-validated non-animal and in vitro tests as they become available.
Acute delayed neurotoxicity - hen	870.6100	Delayed neurotoxicity (acute) – hen	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data. We encourage the substitution of the acute toxicity battery of tests with NICEATM-validated non-animal and in vitro tests as they become available.
none	870.6200	Acute neurotoxicity - rat	New	We encourage the substitution of the acute toxicity battery of tests with NICEATM-validated non-animal and in vitro tests as they become available.

Subchronic				
Current requirement	*Guideline*	*Proposed requirement*	*Change*	*Comment*
90-day Feeding	870.3100	90-day Feeding	Requirement	We suggest additional inclusion of studies using

- rodent		- rodent	modified to include 2 rodent species	the end-use product (EP), to provide useful data.
90-day Feeding – non-rodent	870.3150	90-day Feeding – non-rodent	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
21-day Dermal	870.3200	21- to 28-day Dermal	Changed from CR to R for all food uses. Not required for non-food uses.	This is generally needed for worker risk assessments, and is proposed to be "tailored to the potential for worker exposure" (FRnotice). It is not clear what "tailored" means, but appears to be a way to avoid a clear requirement for the study. We recommend that the 90-day dermal study be extended to a required study for both food and non-food uses. Worker exposure must be evaluated in both cases.
90-day Dermal	870.3250	90-day Dermal	Changed from CR to R for all non-food uses.	This would be required for non-food uses if the dermal route is the major route of exposure. We recommend that this be required for food and non-food uses, to facilitate an assessment of worker exposure in both cases.
90-day Inhalation	870.3465	90-day Inhalation - rat	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data. We urge EPA to require inhalation toxicity studies for all pesticides with vapor pressures greater than 10^{-5} mm Hg.
90-day Neurotoxicity - mammal	870.6200	90-day Neurotoxicity - rat	Changed from CR to R	We support the requirement for this study. We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
90-day Neurotoxicity - hen	870.6100	28-day Neurotoxicity - hen	New - conditional requirement. Replaces 90-day neurotoxicity hen study	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.

Chronic				
Current requirement	*Guideline*	*Proposed requirement*	*Change*	*Comment*
Chronic feeding – rodent and nonrodent	870.4100	Chronic feeding – rodent and nonrodent	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
Oncogenicity – rat and mouse, preferred	870.6100	Carcinogenicity – rat and mouse, preferred	Changed name. Proposed requirement to perform range-finding studies	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.

Developmental Toxicity & Reproduction				
Current requirement	*Guideline*	*Proposed requirement*	*Change*	*Comment*
Teratogenicity – 2 species	870.3700	Prenatal developmental toxicity – rat and rabbit, preferred	Changed name. Testing required on a second species for food and nonfood uses	We support the proposed changes, and suggest the following additional improvements: • include exposures beginning before conception, instead of just beginning at day 6 post-conception, to capture first trimester effects • perform additional testing of postnatal effects resulting from gestational and postnatal exposures to the test agent • evaluate paternally-mediated developmental effects on offspring • ensure that histological methods are used that distinguish between full litter resorption and non-gravid uteri We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
Reproduction – 2 generation	870.3800	Reproduction	Changed from CR to R for nonfood uses based on potential exposure.	We support the requirement for this test, with the following suggestions for improvement: • all doses and controls should be assessed for sperm parameters, including the lowest doses • multiple sites of sperm collection should be considered, and standardized • accurately identify implantation and resorption sites • examine F2 generation for sexual function and fertility We suggest additional inclusion of studies using the end-use product (EP), to provide useful data. We suggest that EPA add language specifying that it approves the use of data from the open literature when it is available.
None	870.6300	Developmental neurotoxicity	New – conditional requirement science-based approach to testing.	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data. We suggest that EPA add language specifying that it approves the use of data from the open literature when it is available.

Comments on Developmental Toxicity and Reproduction Studies:

The EPA description of the developmental toxicity and reproduction studies reads as follows: "The developmental toxicity study is designed to determine the potential of the test substance to induce structural and/or other abnormalities to the fetus as the result of exposure of the mother during pregnancy. Two-generation reproduction testing is designed to provide information concerning the general effects of a test substance on gonadal function, estrus cycles, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring. The study may also provide information about the effects of the test substance on neonatal morbidity, mortality, and preliminary data on teratogenesis and serve as a guide for subsequent tests." (FR, p. 12334) The word "function" is used only once in this paragraph in relation to gonads. EPA leaves out the function of the other organs such as the heart and lungs as well as the other endocrine organs, such as the pancreas, adrenals, and CNS. As knowledge has increased about functional end points, so has knowledge about the significant increases in human disorders that were once considered rare and now have tremendous social and economic impacts on society. Strengthening this paragraph would be an important step toward addressing these considerations in testing protocols. In other words, the testing would be more sensitive to real world damage that has been missed to date.

We strongly support the combined study protocol proposed by EPA. Such combined study protocols are expected to reduce replication of studies, reduce the number of animals to be sacrificed, and most important, introduce the concept of concomitant damage across a number of systems. As EPA begins to look "holistically" at the damage in an animal it will begin to produce data that better explains the manifestation of disease. Using this approach a very realistic picture of the damage caused by a pesticide will be available which should match better what is happening in humans. Ultimately in the end, more causal relationships are likely to be revealed. EPA should turn to the open literature for guidance when selecting the new endpoints for evaluation in the combined assays. We suggest that more functional and histological endpoints need to be incorporated.

Comments on Prenatal Developmental Toxicity Study (870.3700):

Changing the name of this requirement to Prenatal Developmental Toxicity was a positive step forward. It acknowledges that over the past decade, the open (peer-reviewed) literature has exploded with evidence of pesticide damage to the embryo, fetus, and neonate, revealing lesions that heretofore were overlooked by past testing protocols. We suggest that the language in this section should be reinforced where EPA suggests using "…an information based approach…which utilizes the best available knowledge on the chemical…" by clearly adding that EPA approves the use of data from the open literature when it is available. New study protocols and testing strategies are badly needed and this rich source of information should be utilized so that EPA can move forward immediately.

The prenatal developmental toxicity study is designed to provide data on the effects of exposures during gestation. The test chemical is administered to pregnant females (rat or rabbit preferred) from implantation through the gestational period, and then the fetus is examined for visceral and skeletal abnormalities prior to birth. The test is not designed to assess affects from exposures after birth, and does not assess the post-natal effects of gestational exposures. We therefore suggest that a test of postnatal developmental toxicity also be performed.

While it is generally agreed that laboratory animal models are highly predictive of human responses to environmental toxicants, there have been reports in the scientific literature demonstrating that humans may be more sensitive than routine test animals to some developmental toxicants. Examples of such test agents include thalidomide, methotrexate, valproic acid, and isotretinoin.[8 9] The unique sensitivity of humans to developmental toxicants may be due to the relatively long period of rapid development in human infants, continuing through gestation and for several years postnatally. This demonstrates the need to assess the post-natal effect of gestational exposures, and to assess the long-term effects of postnatal exposures to developmental toxicants.

Some developmental toxicants are known to mediate their effects through exposure of the male parent. For example, exposure of fathers to ionizing radiation and chemotherapy treatment is associated with developmental malformation in offspring.[10] Abnormal sperm activity or number has also been associated with pesticide exposures.[11] In 2003, research in Missouri reported that men from Missouri with high levels of alachlor were significantly more likely to have poor semen quality than were men with low levels (odds ratios (ORs) = 30.0), as were men with atrazine levels higher than the limit of detection (OR = 11.3).[12] Unfortunately, male-mediated developmental effects on offspring are not considered in the current guidelines for developmental toxicity testing.[13]

Comments on Reproduction and 2-Generation (fertility) Test (870.3800):

Sexual development, function, and fertility are endpoints reached after a series of dependent and complex processes that include the development and maturation of the sexual organs, maintenance of a normal hormonal milieu, development of appropriate sexual behavior, production of functional gametes, and the capacity for maintaining normal pregnancy and gestation in the female. Disruption of any of these processes may impair or prevent a healthy pregnancy. Here we suggest some improvements for enhancing effectiveness of the reproduction and fertility testing guidelines, as discussed in an article by Claudio et al (1999): [14]

- Low dose effects: The EPA reproduction and 2-generation (fertility) testing guideline requires that only the control and high-dose animals be assessed for sperm parameters. This ignores data demonstrating that with many endocrine disrupting chemicals the effects at low doses may be more severe, and different, from those at higher doses. This bimodal mechanism must be considered when endocrine disrupting chemicals are being tested that may affect fertility outcomes.
- Sperm analysis: The site of sperm collection may affect the parameters of the sample collected, such as motility, morphology, and sperm number. In addition, inter-laboratory variation may be significant. Therefore, the protocols for sperm collection and sample preparation (histological fixation and staining methods, etc.) should be documented, and standardized if possible. Nonetheless, results of these tests may underestimate the impact of toxic chemicals on fertility, since a reduction in sperm number or activity may impact humans far more than rodents; rodents may exhibit normal fertility even when sperm counts have been depleted by 90%.
- Uteri analysis: Although the testing guidelines require identification of implantation and resorption sites in the uterus, we recommend that this be required to be performed using a standardized and effective method, such as staining with ammonium sulfide, and without counter-stain, in order to distinguish between non-gravid uteri and full litter resorption.
- Controls: The results and interpretation of results can vary significantly between laboratories and even between observers from the same laboratory. Therefore, we recommend that the guidelines specify that laboratories provide data from both historic and concurrent positive controls conducted with known reproductive toxicants, for comparison with experimental preparations.
- Second generation effects: Some reproductive toxicants may have more pronounced effects on the second generation; for example, those toxicants that impair female gametes during their formation. Because the female gametes develop early in the second trimester, a pregnant mother nurtures both her developing daughter, and the eggs that will form her future grandchildren. The testing guidelines would be more effective in detecting second generation (F2) effects if they required that the F2 animals (those treated in utero) were grown up and tested for sexual and reproductive dysfunction.
- Metabolism and pharmacokinetics: It may be useful to study early-life stage metabolism and pharmacokinetic parameters, prior to initiation of reproductive testing, to help define an effective dose-range that is most likely to capture toxic effects where/when they may occur.

Improvements in the methods and data interpretation of these protocols should be considered in the future development of testing guidelines, so as to maximize the chance of observing toxic effects where they occur. This should include careful consideration of testing methods that capture early life stages and possible second generation effects.

Mutagenicity				
Current requirement	*Guideline*	*Proposed requirement*	*Change*	*Comment*
Gene mutation	870.5100	Bacterial reverse mutation assay	Replaces current mutagenicity battery	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
Structural chromosome	870.5300 870.5375	In vitro mammalian cell	Replaces current	We suggest additional inclusion of studies using the end-use product (EP), to provide

aberration		assay	mutagenicity battery	useful data.
Other genotoxic effects	870.5385 870.5395	In vivo cytogenetics	Replaces current mutagenicity battery	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
		Other mutagenicity studies	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.

Special Testing				
Current requirement	*Guideline*	*Proposed requirement*	*Change*	*Comment*
General metabolism	870.7485	General metabolism	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
Dermal penetration	870.7600	Dermal penetration	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
Domestic animal safety	870.7200	Companion animal safety	No changes	We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
None	870.6500	Scheduled controlled operant behavior	Replaces current neurotoxicity battery	We support the requirement for this study. We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
None	870.6850	Peripheral nerve function	Replaces current neurotoxicity battery	We support the requirement for this study. We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
None	870.6855	Neurophysiology: Sensory evoked potentials	Replaces current neurotoxicity battery	We support the requirement for this study. We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.
None	870.7800	Immunotoxicity	New requirement. Required for food uses and nonfood uses.	We strongly support the inclusion of this study in the required battery of tests. We suggest additional inclusion of studies using the end-use product (EP), to provide useful data.

Comments on Thyroid Testing Protocols (FR, p. 12296):

The EPA discussion of thyroid testing protocols is an important step forward (FR, pg. 12296). EPA appropriately emphasizes the importance of capturing any sign of developmental thyroid impairment. However, it has been demonstrated repeatedly, that even within what is considered the normal range for the suite of thyroid hormones, reduced intelligence and behavioral changes are possible if the mothers' thyroid hormone titers were in what is considered low normal. [15] It is imperative that thyroid histopathology is required in every protocol that doses animals. We encourage the Agency to move forward with these plans.

Prominent researchers with decades of experience with toxicity of hormone disrupting chemicals have recently raised strong concerns that traditional toxicity testing methods are likely to overlook toxic impacts of this class of chemicals, and underestimate their ecological and human health impacts. A recent publication states the reasons for this as follows: "Information concerning the fundamental mechanisms of action of both natural and environmental hormones, combined with information concerning endogenous hormone concentrations, reveals how endocrine-disrupting chemicals with estrogenic activity (EEDCs) can be active at concentrations far below those currently being tested in toxicological studies. Using only very high doses in toxicological studies of EEDCs thus can dramatically underestimate bioactivity. Specifically: *a*) The hormonal action mechanisms and the physiology of delivery of EEDCs predict with accuracy the low-dose ranges of biological activity, which have been missed by traditional toxicological testing. *b*) Toxicology assumes that it is valid to extrapolate linearly from high doses over a very wide dose range to predict responses at doses within the physiological range of receptor occupancy for an EEDC; however, because receptor-mediated responses saturate, this assumption is invalid. *c*) Furthermore, receptor-mediated responses can first increase and then decrease as dose increases, contradicting the assumption that dose-response relationships are monotonic. *d*) Exogenous estrogens modulate a system that is physiologically active and thus is already above threshold, contradicting the traditional toxicological assumption of thresholds for endocrine responses to EEDCs."[16] These and other prominent researchers call for the inclusion of testing endpoints that include, "more sensitive, less visible end points such as osteoporosis, increased risk for cardiovascular disease, or cognitive changes."[17].

Comments on Nontarget Plant Protection Studies (FR, p. 12298):

We are concerned that the proposed data requirements for nontarget plant protection studies do not adequately reflect current scientific information in two major respects. First, there is no requirement that the tests be performed on a broad range of species. Second, there is no requirement that tests include the reproductive phase of the plant's life cycle. We therefore recommend the following changes:

1) EPA should increase the range of species tested in nontarget plant protection studies. The proposed data requirements leave unchanged EPA's current practice of requiring terrestrial plant testing on only ten species. All of these ten species are annual agricultural flowering plant species. Yet, these ten species are considered by the agency as surrogates for the 16000 native plant species in the U.S. For example, hardwood trees, native shrubs, conifers, native grasses, and ferns are all completely ignored.
2) EPA should increase the duration of nontarget plant protection and include reproductive endpoints (endpoints that measure yield of fruit and seed). Low dose, high potency herbicides such as acetolactase synthase inhibitors have been the subject of research over the last two decades because they move off target sites in water, on soil particles, and as spray drift and have caused reproductive injury to plants at herbicide concentrations so low that did not produce visible leaf injury. This kind of effect can have ecosystem-level effects, but is currently ignored by plant protection data requirements, in which the maximum test length is 28 days, too short to capture the reproductive phase of most species.

Comments on Endangered Species Assessments and Determinations (FR, p. 12291-12292)

We suggest that EPA require the following data to effectively characterize potential risks to listed endangered species from pesticide use:

1) Accurate estimates of aquatic exposure: EPA's estimates for aquatic exposure estimation are flawed. EPA's screening level assessment tool, GENEEC, assumes an application to a 10-hectare field that drains into a one-hectare pond. This model is likely to underestimate concentrations in a number of scenarios. EPA assumes a single application in a watershed. This assumption often does not reflect real-world scenarios. Rather, it is likely

that applications are clustered in each watershed, with similar crops and similar pesticide uses occurring close together. EPA's models also assume that the pesticide concentration will be the same throughout the water body, where in reality the concentration is likely to be highest at the water surface and at the edge of the water body. In addition, many listed species use water bodies smaller than 10 hectares, and concentrations are likely to be higher in those water bodies.

2) Accurate estimates of pesticide concentrations in urban streams, where runoff patterns vary widely from natural systems: Use of EPA's typical models can be expected to generate estimates that are poorly predictive of actual stream concentrations.
3) Accurate estimates of exposure of terrestrial species: EPA only considers ingestion exposures. This fails to capture inhalation and dermal exposures.
4) Identification of critical sublethal endpoints: EPA bases its analysis of effects almost completely on comparisons between lethal concentrations necessary to kill half a test population (LC50) and expected environmental levels based on modeling. For fish, EPA risk assessments conclude that a level of concern (LOC) is exceeded for endangered fish species if the expected concentration is more than 1/20th of the LC50 value. However, there is increasing evidence that sublethal effects on fish and wildlife can be significant and can affect populations as well as individuals. Effects include immune system suppression, hormone disruption, behavioral changes, mutagenicity, carcinogenicity, transgenerational changes, and others. Currently, testing of sublethal effects consists only of "life cycle" tests to determine effects on growth and reproduction; these tests, however, are only occasionally required.
5) Quantification of indirect effects, such as effects on the food supply or on habitat: Reductions in habitat or food supply can be as deleterious to the survival of a listed species as acute lethality; however, current testing is inadequate, and does not capture these effects.
6) Identification of synergistic effects: In particular, data is needed to assess the effects of other active ingredients, inert ingredients, adjuvants, and degradates in combination with the active ingredient under review. Water quality studies repeatedly show that multiple pesticides are found in salmon habitat, and many of these pesticides have the same modes of action and are known to affect the same organ systems, conditions which require a default assumption of additivity. Inert ingredients and adjuvants are used in or with almost every pesticide product, so exposures to the combination of active ingredient(s) plus inert ingredients or adjuvants is common. Similarly, co-exposure of active ingredients and their degradates is common, and should be better captured in current testing protocols.

Non-target organisms				
Current requirement	*Guideline*	*Proposed requirement*	*Change*	*Comment*
Avian Oral LD_{50}	850.2100	Avian oral toxicity	Added testing on a second species (passerine) for some uses. Expanded requirement to include testing with the TEP. Clarified test note to better identify when this test requirement is applicable.	We encourage the use of at least two species for all uses, and expand the test to three species for compounds with acute oral LD50s of 500 mg/kg or less.
Avian reproduction	850.2300	Avian reproduction	Changed from ''conditionally required'' to ''required'' for	We support the requirement for this study. We encourage the development of avian reproduction tests with a passerine species in addition to mallards and bobwhite quail for

			terrestrial, aquatic food, aquatic nonfood outdoor, forestry, and residential outdoor uses.	terrestrial, aquatic food, aquatic nonfood outdoor, forestry, and residential outdoor uses. We encourage better harmonization with OECD in the use of Japanese Quail for this test as an alternate to Bobwhite Quail
Simulated or actual field testing-mammals and birds	850.2500	Simulated or actual field testing	Expanded conditional requirement to terrestrial feed and aquatic nonfood outdoor uses. Added independent laboratory validation of methods.	We support the expansion of the conditional requirement for this study, and support the independent validation of laboratory methods.

Comments on Nontarget Organisms Data Requirements (FR, p. 12288-12292):

The Avian Oral LD50 Test 850.2100 is designed to evaluate acute toxicity to birds using one or two species of birds (preferred red-winged blackird, mallard, and/or bobwhite quail). Because of the wide sensitivity range of avian species to oral toxicants[18], testing with additional species will decrease uncertainty in toxicity estimates. We recommend using red-winged blackbirds for all testing in addition to mallards or bobwhite quail.

The Avian Reproduction Test 850-2300 currently uses only precocial species whose eggs are artificially incubated. Many toxicants influence incubation behavior, and natural incubation and parental rearing of chicks is a much more sensitive test of effects on reproduction. No current testing protocols have been developed for passerine species, and we encourage the EPA to support studies to develop passerine reproductive testing with a species such as Zebra Finch or House Finch.

We realize that the additional tests will require the use of additional animals, but we are convinced that at this time the toxicity information cannot be learned in any other way, because of high variability between avian species. We support reducing the number of animals used in testing, only if the statistical power of the test is maintained, and rigorous analysis of the statistical power of all test is conducted prior to testing, and prior to changing any test so that fewer animals are used. We do not support arbitrarily reducing the number of animals tested if the value of the test is reduced.

Comments on Post-Application Exposure Assessment (Sub-part K. 158.800, FR, p. 12299)

We applaud EPA's commitment to requiring more comprehensive data on post-application exposures, especially inhalation exposures. With more suburbs expanding into farmland, bystander inhalation exposure from both spray drift and volatilization drift is becoming an increasing problem that needs more attention from EPA. Data from the California Air Resources Board (CARB) air monitoring program conducted in conjunction with the California Department of Pesticide Regulation (CDPR) indicates that pesticides with vapor pressures greater than 10^{-6} mm Hg have significant potential for off-site vapor drift through post-application volatilization.[19] Analysis of the ARB reports and comparison of measured air concentrations to Reference Exposure Levels derived from available Reference Doses or Reference Concentrations indicates that inhalation exposures may exceed "acceptable" levels for acute exposures, especially for children and other vulnerable populations living in agricultural areas.[20] Work done by the California Dept. of Health Services indicates that even seasonal exposures exceed "acceptable" sub-chronic levels for a number of pesticides in areas of high pesticide use during seasons of high use.[21] For some pesticides, inhalation exposures may comprise a substantial fraction of the total exposure which EPA currently does not evaluate for non-fumigant pesticides. The Food Quality Protection Act explicitly states that EPA-OPP is required to consider aggregate exposure to a chemical and that any tolerances deemed "safe" for children meet the following definition as stated in Section 408, which reads:

> "DETERMINATION OF SAFETY.—As used in this section, the term "safe" with respect to a tolerance for a pesticide chemical residue, means that the Administrator has determined that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."

We urge EPA to use the existing information collected by the CA Air Resources Board, and in addition to require inhalation exposure monitoring that captures volatilization drift for new registrations or re-registrations. Vapor pressure of the active ingredient coupled with half-life provides an unbiased means of determining which pesticides are likely to be most problematic.

Inhalation exposure	875.2500	Inhalation exposure	Changed from ''conditionally required'' to ''required''. Expanded use sites to include testing for greenhouses, nurseries, forests, residential settings, golf courses and certain indoor environments.	We support the change from conditionally required to required and recommend that vapor pressure and half-life be used as a guide to flag potentially problematic chemicals early in the risk assessment process.

Comments on EPA's Proposal About The Confidentiality of Safety and Efficacy Information (FR, p. 12284-12285)

EPA has proposed that all information submitted in accordance with part 158 after May 4, 1988 (except information pertaining to a pesticide that has never been registered) will be deemed non-confidential without further notice to the submitter unless it has been designated as confidential. EPA makes this proposal in accordance with 40 CFR 158.33. We support EPA's proposal. In addition, in order to be in compliance with the decision in *NCAP v. Browne*r 941 F. Supp. 197, 201 (D.D.C. 1996), EPA must require that submitters provide a substantiation of any confidentiality claims made. In *NCAP v. Browner*, with reference to confidentiality claims, the court stated "the burden of proving that the circumstances justify nondisclosure falls upon the party seeking to avoid disclosure." Justifications of confidentiality claims under FIFRA 10(d)(1) must meet a stringent standard. In *NCAP v. Browner* the court stated that the "party [seeking to avoid disclosure] need not demonstrate actual harm but must show, (1) actual competition, and (2) a likelihood of substantial competitive injury. Conclusory and generalized allegations do not sustain the burden of nondisclosure under FOIA." EPA must receive and evaluate substantiations of any confidentiality claims in order to determine that this standard has been met. Further, in order to comply with the public disclosure intent of FIFRA 10(d)(1), we request that confidentiality justifications be provided to the public when information that has been designated as confidential is requested.

EPA Needs to Include Tests of Inert Ingredients, Degradates, and Combinations

In order to provide more accurate, real-world assessments, data is urgently needed to assess the effects of other active ingredients, inert ingredients, adjuvants, and degradates in combination with the active ingredient under review. Inerts, which often comprise the bulk of the pesticide formulation, may be added to improve the efficacy of the product, for example, by helping the active ingredient dissolve, easing application, or improving the pesticide's adherence to plant leaves. Unfortunately, these same properties may also increase the toxicity of the formulation, render it more bioavailable, increase solubility, or enhance the toxicity of the active ingredient. EPA has four lists of inert ingredients: inerts of toxicological concern, potentially toxic inerts, inerts of unknown toxicity, and minimal-risk inerts. Of the more than 1800 chemicals on EPA's list of inerts of unknown toxicity, 75 are identified as hazardous by the Clean Air Act, 52 under Superfund, 64 in the Clean Water Act, 43 on the Toxics Release Inventory, and 78 with the Toxic Substances Control Act. In addition, 292 inerts of unknown toxicity are registered by EPA as active ingredients in other pesticides. Currently, EPA does not require toxicity information for these inert ingredients. [22] A recent article reported that PBO (piperonyl butoxide), an inert ingredient that makes pyrethroid pesticides 10x more lethal to black flies and mosquitoes, also enhances the toxicity of these pesticides to fish. However, EPA's recent assessment of PBO[23] failed to assess the toxicity of PBO in conjunction with the active ingredient.[24]

Water quality studies repeatedly show that multiple pesticides are found in salmon habitat, and many of these pesticides have the same modes of action and are known to affect the same organ systems, conditions which require a default assumption of additivity. Inert ingredients and adjuvants are used in or with almost every pesticide product, so

exposures to the combination of active ingredient(s) plus inert ingredients or adjuvants is common. Similarly, co-exposure of active ingredients and their degradates is common, and should be better captured in current testing protocols.

EPA Should Terminate its Collaborative Work with ILSI (FR, p. 12313)

We are extremely concerned about EPA meetings with the International Life Sciences Institute (ILSI) regarding evaluation of pesticide testing paradigms. The FR notice states that, "The Health and Environmental Sciences Institute (HESI)/International Life Sciences Institute initiated a project in 2001 titled, "Developing Strategies for Agricultural Safety Evaluation. The purpose of this project was to bring together scientific experts from government, academia and industry, including the international community to determine whether the current testing paradigm for pesticide chemicals could be made more efficient and accurate. Agency scientists from EPA's Office of Pesticide Programs and Office of Research and Development are involved in this project" (FR, p. 12313). We note with alarm that there is an absence of public interest representatives in these ILSI-EPA discussions. The ILSI is clearly representative of industry interests. Their membership is all corporations, including many chemical and pesticide manufacturers:

> ILSI Health and Environmental Sciences Institute members:
> 3M Pharmaceuticals, Abbott Laboratories, Altana Pharma AG, Amgen, Inc., AstraZeneca AB, ATOFINA Chemicals, Inc., Aventis Pharmaceuticals, BASF Corporation, Bayer AG, Berlex Laboratories, Inc. Biogen Idec MA Inc., Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Dow AgroSciences/The Dow Chemical Company, E.I. du Pont de Nemours and Company, Eastman Kodak Company, Eisai Co., Ltd., Eli Lilly and Company, Endo Pharmaceuticals, ExxonMobil Biomedical Sciences, GlaxoSmithKline, Hoffmann-La Roche, Inc., Institute de Recherches Int. Servier, Johnson & Johnson Pharmaceuticals, L'Oreal Corporation, Meiji Seika Kaisha, Ltd., Merck & Co., Inc., Mitsubishi Pharma Corporation, Monsanto Company, N.V. Organon, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Pfizer Inc., The Procter & Gamble Company,Purdue Pharma L.P., Rohm and Haas Company, Sankyo Co., Ltd., Sanofi-Synthelabo Inc., Schering-Plough Research Institute, Solvay Pharmaceuticals GmbH, Sumitomo Chemical Co., Ltd., Syngenta, Tanabe Seiyaku Co., Ltd., U.S. Borax, Inc., Valent U.S.A. Corporation, Wyeth Research

According to their Spring 2004 newsletter (Vol 3, Number 1), *HESI News*, the 2004 ILSI-HESI Executive Committee is comprised of numerous corporate and chemical industry representatives:

> Dr. Helmut H. Greim, Chair, *Technical University of Munich***;** Dr. Lewis L. Smith, P resident, *Syngenta Ltd.***;** Dr. Samuel M. Cohen, Vice Chair, *University of Nebraska Medical Center***;** Dr. William T. Robinson, Vice President, *Novartis Pharmaceuticals Corporation***;** Dr. Jay I. Goodman, Member-at-Large (Past Chair), *Michigan State University;* Dr. Robert W. Rickard, Treasurer, *DuPont Haskell Laboratory;* Dr. Elaine M. Faustman, Secretary, *University of Washington;* Dr. Craig H. Farr, Member at Large, *ATOFINA Chemicals, Inc.;* Dr. Ronald N. Hines, Member at Large, *Medical College of Wisconsin;* Dr. James S. MacDonald, Member at Large, *Schering-Plough Research Institute.*

The work that EPA is conducting with ILSI and with ILSI-HESI does not include any opportunities for meaningful public participation, and does not include public interest representatives. It is essentially a government-corporate partnership. ILSI is an industry funded organization. The scientific panels it assembles under the cooperative agreement with EPA do not operate in accordance with the Federal Advisory Committee Act (FACA) rules, and are often imbalanced. The regulated community typically has had a disproportionate voice on these panels where the outcome will impact future EPA policy on how the risks from pesticides are assessed and regulated. In addition to the serious imbalances in committee membership, ILSI panels fail to operate in accordance with the open government (e.g. notice and open meetings) requirements of FACA. The ILSI panels and many aspects of their deliberations therefore fail to provide the kind of transparency that has formed the focus for discussion on the Scientific Advisory Panels (SAP), and Pesticide Policy Dialogue Committee (PPDC). Transparency must be a two–way process. As it stands, the science policy discussions within ILSI panels often take place behind a one–way mirror, with the public and the public interest community shut out of meaningful participation. We therefore recommend that EPA terminate its collaborative working relationship with ILSI and other industry trade groups, and recognize that public representation and meaningful participation is a key component of a credible process. Without transparency, it is likely that both the process and any work products arising from the process will be subject to public mistrust and possibly rejection.

CONCLUSION:

While we offer suggestions and, in some cases, raise serious concerns regarding current and proposed testing protocols, we applaud efforts by EPA to document the current and proposed testing requirements and for careful consideration by EPA of these comments. We share the goals of EPA scientific and technical staff to develop testing protocols that are as informative as possible, feasible, cost-effective, and validated. We share the goals of the EPA Administrator and the Office of Prevention, Pesticides and Toxic Substances (OPPTS) to, "*regulate pesticides and chemicals to ensure protection of public health and the environment, as well as promote innovative programs to prevent pollution*".[25] We stand ready to work with the EPA, OPPTS, and the Office of Pesticides to fulfill this shared goal.

Thank you for your consideration of these comments,

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[1] US EPA Office of Prevention, Pesticides and Toxic Substances. Home website: http://www.epa.gov/oppts/index.htm

[2] Huff J. 1994. Chemicals causally associated with cancers in humans and in laboratory animals: a perfect concordance. In: Waalkes MP, Ward JM (Eds.), Carcinogenesis. Raven Press, New York. Pp. 25-37

[3] Huff J. 1993. Chemicals and cancer in humans: first evidence in experimental animals. Env Health Perspect, 100: 201-210

[4] Haseman et al. 2001. op cit.

[5] Bortolozzi AA, Duffard RO, Evangelista de Duffard AM. 1999. Behavioral alterations induced in rats by a pre- and postnatal exposure to 2,4-dichlorophenoxyacetic acid. Neurotoxicol Teratol 21(4):451-465.

Qiao D, Seidler FJ, Abreu-Villaca Y, Tate CA, Cousins MM, Slotkin TA. 2004. Chlorpyrifos exposure during neurulation: cholinergic synaptic dysfunction and cellular alterations in brain regions at adolescence and adulthood. Brain Res Dev Brain Res 148(1):43-52.

Slotkin TA. 2004. Guidelines for developmental neurotoxicity and their impact on organophosphate pesticides: A personal view from an academic perspective. Neurotoxicology 25(4):631-640.

[6] Ahmadi FA, Linseman DA, Grammatopoulos TN, Jones SM, Bouchard RJ, Freed CR, Heidenreich KA, Zawada WM. 2003. The pesticide rotenone induces caspase-3-mediated apoptosis in ventral mesencephalic dopaminergic neurons. J Neurochem 87:914-921.

Aldridge JE, Seidler FJ, Meyer A, Thillai I, Slotkin TA. 2003. Serotonergic systems targeted by developmental exposure to chlorpyrifos: Effects during different critical periods. Environ Health Perspect 111:1736-1743.

Aldridge JE, Seidler FJ, Slotkin TA. 2004. Developmental exposure to chlorpyrifos elicits sex-selective alterations of serotonergic synaptic function in adulthood: Critical periods and regional selectivity for effects on the serotonin transporter, receptor subtypes, and cell signaling. Environ Health Perspect 112:148-155.

Goldman JM, Stoker TE, Cooper RL, McElroy WK, Hein JF. 1994. Metam sodium suppresses the hormonal control of ovulation in the rat: Relationship to changes in hypothalamic catecholamines. Toxicologist 14:77.

Kitazawa M, Anantharam V, Kanthasamy A, Kanthasamy AG. 2004. Dieldrin promotes proteolytic cleavage of poly(ADP-ribose) polymerase and apoptosis in dopaminergic cells: protective effect of mitochondrial anti-apoptotic protein Bcl-2. Neurotoxicology 25:589-598.

Kitazawa M, Anantharam V, Kanthasamy AG. 2001. Dieldrin-induced oxidative stress and neurochemical changes contribute to apoptopic cell death in dopaminergic cells. Free Radic Biol Med 31:1473-1485.

Mohammad FK, St.Omer VEV. 1988. Effects of prenatal exposure to 2,4-D/2,4,5-T mixture on postnatal changes in rat brain glutamate, GABA, protein, and nucleic acid levels. Bull Environ Contam Toxicol 40:294-300.

Reeves R, Thiruchelvam M, Richfield EK, Cory-Slechta DA. 2003. Behavioral sensitization and long-term neurochemical alterations associated with the fungicide triadimefon. Pharmacol Biochem Behav 76:315-326.

Rivera S, Rosa R, Martinez E, Sunol C, Serrano MT , Vendrell M, et al. 1998. Behavioral and monoaminergic changes after lindane exposure in developing rats. Neurotoxicol Teratol 20:155-160.

Thiruchelvam M, McCormack A, Richfield EK, Baggs RB, Tank AW, Di Monte DA, et al. 2003. Age-related irreversible

progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype. Eur J Neurosci 18:589-600.

Thiruchelvam M, Richfield EK, Goodman BM, Baggs RB, Cory-Slechta DA. 2002. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotoxicology 23:621-633.

[7] The National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) created the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM or "the Center") in 1998. The Center organizes meetings and workshops for the development, review, and validation of alternative toxicological testing methods. http://iccvam.niehs.nih.gov/home.htm

[8] Schardein JL, Keller KA. Potential human developmental toxicants and the role of animal testing in their identification and characterization. Crit Rev Toxicol. 1989;19(3):251-339. Review.

[9] Newman LM, Johnson EM, Staples RE. Assessment of the effectiveness of animal developmental toxicity testing for human safety. Reprod Toxicol. 1993 Jul-Aug;7(4):359-90. Review.

[10] Marchetti F, Wyrobek AJ. Mechanisms and consequences of paternally-transmitted chromosomal abnormalities. Birth Defects Res C Embryo Today. 2005 Jun;75(2):112-29.

Silver EW, Eskenazi B, Evenson DP, Block G, Young S, Wyrobek AJ. Effect of antioxidant intake on sperm chromatin stability in healthy nonsmoking men. J Androl. 2005 Jul-Aug;26(4):550-6.

Wyrobek AJ, Schmid TE, Marchetti F. Relative susceptibilities of male germ cells to genetic defects induced by cancer chemotherapies. J Natl Cancer Inst Monogr. 2005;(34):31-5. Review.

Eskenazi B, Kidd SA, Marks AR, Sloter E, Block G, Wyrobek AJ. Antioxidant intake is associated with semen quality in healthy men.Hum Reprod. 2005 Apr;20(4):1006-12. Epub 2005 Jan 21.

[11] Swan SH. Semen quality in relation to pesticide exposure in Missouri males. Mo Med. 2003 Nov-Dec;100(6):554. No abstract available.

Fenster L, Waller K, Windham G, Henneman T, Anderson M, Mendola P, Overstreet JW, Swan SH. Trihalomethane levels in home tap water and semen quality. Epidemiology. 2003 Nov;14(6):650-8.

Swan SH, Kruse RL, Liu F, Barr DB, Drobnis EZ, Redmon JB, Wang C, Brazil C, Overstreet JW; Study for Future Families Research Group. Semen quality in relation to biomarkers of pesticide exposure. Environ Health Perspect. 2003 Sep;111(12):1478-84.

[12] Swan SH, Kruse RL, Liu F, Barr DB, Drobnis EZ, Redmon JB, Wang C, Brazil C, Overstreet JW; Study for Future Families Research Group. Semen quality in relation to biomarkers of pesticide exposure. Environ Health Perspect. 2003 Sep;111(12):1478-84.

[13] Claudio L, Bearer CF, Wallinga D. Assessment of the U.S. Environmental Protection Agency methods for identification of hazards to developing organisms, Part II: The developmental toxicity testing guideline. Am J Ind Med. 1999 Jun;35(6):554-63. Review.

[14] Claudio L, Bearer CF, Wallinga D. Assessment of the U.S. Environmental Protection Agency methods for identification of hazards to developing organisms, Part I: The reproduction and fertility testing guidelines. Am J Ind Med. 1999 Jun;35(6):543-53. Review.

[15] Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341(8):549-555.Misc above nontarget plant protection.

[16] Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ Health Perspect. 2003 Jun;111(8):994-1006. Review.

[17] Brucker-Davis F, Thayer K, Colborn T. Significant effects of mild endogenous hormonal changes in humans: considerations for low-dose testing. Environ Health Perspect. 2001 Mar;109 Suppl 1:21-6. Review.

[18] Mineau, P., A. Baril, B.T. Collins , J. Duffe, G. Joerman, R. Luttik. 2001. Reference values for comparing the acute toxicity of pesticides to birds. Reviews of Environmental Contamination and Toxicology 170:13-74.

[19] See California Air Resources Board air monitoring reports at California Department of Pesticide Regulation Toxic Air Contaminant Program web site at http://www.cdpr.ca.gov/docs/empm/pubs/tac/tacstdys.htm.

[20] Kegley, S.E., Katten, A., Moses, M. Secondhand Pesticides: Airborne Pesticide Drift in California, Pesticide Action Network, California Rural Legal Assistance Foundation, Pesticide Education Center and Californians for Pesticide Reform (May, 2003), http://www.panna.org/resources/documents/secondhandDriftAvail.dv.html.

[21] S. Lee, R. McLaughlin, M. Harnly, et al., Community exposures to airborne agricultural pesticides in California: Ranking of Inhalation Risks, Env Health Persp, 2002, 110: 1175–84.

[22] Renner, R. Are pesticide “inerts” an unrecognized environmental danger? Scientists question the continued use of POEA in Roundup, citing data showing harmful effects to frogs. Env Sci Tech, Sept 7, 2005. http://pubs.acs.org/subscribe/journals/esthag-w/2005/sep/science/rr_inerts.html

[23] http://docket.epa.gov/edkpub/do/EDKStaffCollectionDetailView?objectId=0b0007d4805d36b9

[24] Renner, R. Are pesticide “inerts” an unrecognized environmental danger? Scientists question the continued use of POEA in Roundup, citing data showing harmful effects to frogs. Env Sci Tech, Sept 7, 2005. http://pubs.acs.org/subscribe/journals/esthag-w/2005/sep/science/rr_inerts.html

[25] US EPA Office of Prevention, Pesticides and Toxic Substances. Home website: http://www.epa.gov/oppts/index.htm