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Natural Resources Defense Council

On behalf of our 1.2 million members and online activists, NRDC advocates for disclosure of information, regard for scientific inquiry and facts, justice for disempowered people, honesty by government, and corporate accountability. We seek to establish sustainability and good stewardship of the Earth as central ethical imperatives of human society (www.nrdc.org)

Comments to the FIFRA Scientific Advisory Panel on the EPA Notice of Intent to Cancel Carbofuran
Feb 5-8, 2008

BACKGROUND

The N-methyl carbamates are among the most toxic category of pesticides. For example, the Material Safety Data Sheet (MSDS) provided by the registrant (FMC Corp) for carbofuran warns that "Effects from overexposure result from either swallowing, inhaling or coming into contact with the eyes or skin. Conditions of increased temperature and humidity may aid skin absorption of this product and, therefore, increase toxicity. Symptoms of overexposure include headache, light-headedness, weakness, abdominal cramps, nausea, excessive salivation, perspiration, blurred vision, tearing, pin-point pupils, blue skin color, convulsions, tremor and coma."[1] This is a typical description of the health effects of all the NMC pesticides.

The approximate acute oral dose that is lethal for half of test animals (LD50) following oral dosing to male rats is: 0.5 mg/kg body wt for aldicarb, 2.5 mg/kg for oxamyl, and 5

[1] http://msds.fmc.com/msds/100000010246-msds_us-e.pdf

mg/kg for carbofuran.[2] These pesticides are far more acutely toxic than nicotine (LD50=50 mg/kg), DDT (LD50=100 mg/kg), or ethanol (LD50=5600 mg/kg) by oral dosing. The LD50 for aldicarb (0.5) is only 25-fold less potent than dioxin (0.02 mg/kg; TCDD), the most toxic substance known.

Because it is acutely toxic, fetotoxic, and neurotoxic, and because of the availability of reduced-risk chemicals and non-chemical alternatives, on November 26, 2007, the Natural Resources Defense Council (NRDC) petitioned the U.S. Environmental Protection Agency (EPA) to revoke all tolerances of carbofuran.[3] NRDC and the American Bird Conservancy (ABC) subsequently submitted an amended petition to provide more detailed facts to support NRDC's original petition.[4]

NRDC RESPONSE TO SELECTED CHARGE QUESTIONS

Point of Departure (PoD) and FQPA Safety Factor Determination for Dietary Risk Assessment for Infants and Children

Please comment on whether the scientific evidence currently before the Agency supports the Agency's conclusion that brain AChE data provide a more robust PoD than the RBC AChE data.

NRDC supports the use of whole brain acetyl-cholinesterase (AChE) data as preferable to blood AChE data because whole brain data tends to be more stable (less variation between measurements), and it is a reflection of the target organ of interest for toxicity.

Please also comment on whether the scientific evidence currently before the Agency supports the EPA's conclusion that the Agency's benchmark dose analysis of the brain AChE data from three studies provides a scientifically appropriate basis for assessing carbofuran risk to infants and children.

NRDC supports the Agency's approach to conducting a benchmark dose analysis from the three studies it was provided. However, NRDC disagrees that sole reliance on these AChE data are sufficiently health-protective; this has not been established scientifically. Use of these data fails to identify possible regional effects, non-cholinergic effects, and effects at various time points of development, and is therefore likely to underestimate the toxicity of carbofuran.

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[2] All LD50 values from Sigma Chem Co.

[3] NRDC Petition to Cancel Carbaryl and Propoxur for Pet Collar Uses; Petition to Revoke All Tolerances of Carbofuran; and Comments on EPA's revised cumulative risk assessment for the N-methyl carbamate pesticides Nov. 26, 2007, EPA-HQ-OPP-2007-0935-0027 and -0027.1

[4] NRDC and Am Bird Conservancy Amend Petition to Revoke Import Tolerances of Carbofuran. December 29, 2007. EPA-HQ-OPP-2007-0935

Rigorous independent studies of a related AChE-inhibitor, chlorpyrifos, have demonstrated both cholinergic and non-cholinergic toxicity.[5] Through the non-cholinergic mechanism, chlorpyrifos elicited widespread neural damage, and disrupted cell development. Through the cholinergic mechanism, chlorpyrifos induced apoptosis during neurulation, resulting in reduced cell numbers in brain regions that are enriched in cholinergic neurons. These regional effects would be undetectable in the toxicology protocols used by the Agency to evaluate carbofuran toxicity. Behavioral and cognitive testing, including learning and memory tests, reflex tests, and others, are key to assessing the true toxic effects of any neurotoxic and fetotoxic chemicals.

Most importantly, with any developmental neurotoxic chemical such as carbofuran, effects are the result the dose, the duration of the effect, and the stage of development at which the exposure takes place. Exposures during key windows of susceptibility during neural development, even at very low doses, are most likely to have permanent, devastating effects on neural function, including behavior and cognition (reviewed in Colborn, EHP, 2006[6]). These endpoints are not incorporated into the benchmark dose analysis. Failure to consider these cognitive and neurobehavioral endpoints is likely to result in an underestimation of carbofuran toxicity.

The benchmark dose analysis failed to incorporate the impact of human genetic variability in response to carbofuran. Genetic polymorphisms that impair the activity of paraoxonase 1 (PON1) to hydrolyze AChE can result in abnormally sustained cholinesterase activity. There is a substantial literature database on the variability of

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[5] Slotkin TA, Seidler FJ. Prenatal chlorpyrifos exposure elicits presynaptic serotonergic and dopaminergic hyperactivity at adolescence: critical periods for regional and sex-selective effects. Reprod Toxicol. 2007 Apr-May;23(3):421-7.

Slotkin TA, Tate CA, Ryde IT, Levin ED, Seidler FJ. Organophosphate insecticides target the serotonergic system in developing rat brain regions: disparate effects of diazinon and parathion at doses spanning the threshold for cholinesterase inhibition. Environ Health Perspect. 2006 Oct;114(10):1542-6.

Slotkin TA, Levin ED, Seidler FJ. Comparative developmental neurotoxicity of organophosphate insecticides: effects on brain development are separable from systemic toxicity. Environ Health Perspect. 2006 May;114(5):746-51.

Slotkin TA, Brown KK, Seidler FJ. Developmental exposure of rats to chlorpyrifos elicits sex-selective hyperlipidemia and hyperinsulinemia in adulthood. Environ Health Perspect. 2005 Oct;113(10):1291-4.

Aldridge JE, Meyer A, Seidler FJ, Slotkin TA. Alterations in central nervous system serotonergic and dopaminergic synaptic activity in adulthood after prenatal or neonatal chlorpyrifos exposure. Environ Health Perspect. 2005 Aug;113(8):1027-31.

Slotkin TA, Seidler FJ. The alterations in CNS serotonergic mechanisms caused by neonatal chlorpyrifos exposure are permanent. Brain Res Dev Brain Res. 2005 Aug 8;158(1-2):115-9.

Slotkin TA, Oliver CA, Seidler FJ. Critical periods for the role of oxidative stress in the developmental neurotoxicity of chlorpyrifos and terbutaline, alone or in combination. Brain Res Dev Brain Res. 2005 Jun 30;157(2):172-80.

[6] Colborn T. A case for revisiting the safety of pesticides: a closer look at neurodevelopment. Environ Health Perspect. 2006 Jan;114(1):10-7. Review.

activity of the human paraoxonase 1 (PON1)-mediated detoxification pathway, and most recently a 2006 published study reported that children may be up to 164-fold more sensitive than adults to the toxic impacts of chlorpyrifos and diazinon, based on rigorous assessments of mothers and children of the Salinas Valley, CA (Furlong et al, Pharmacogenetics and Genomics, 2006). [7]

Please comment on whether you agree with the Agency's conclusion that, based on the available scientific evidence, there is remaining uncertainty regarding lack of dose response data at the low end of the dose response curve for RBC AChE inhibition with respect to extrapolating risk to infants and children. Please provide a basis for your conclusion.

NRDC agrees with EPA that there is considerable uncertainty regarding toxicity at the low end of dose response curve for AChEi, particularly with respect to risks resulting from exposure during early life stages. The magnitude of this uncertainty has not been analyzed, and even the contributors to this uncertainty have not been fully documented. For example, the sole reliance on whole brain AChEi data from female adult rodents to calculate a benchmark dose fails to incorporate possible regional effects, non-cholinergic effects, and long-term or permanent effects. Behavioral and cognitive testing, including learning and memory tests, reflex tests, and others, are key to assessing the true toxic effects of any developmental neurotoxic and fetotoxic chemicals.

Experts have warned that, "the fact that alterations in neurodevelopment occur with organophosphate exposures below the threshold for cholinesterase inhibition reinforces the inadequacy of this biomarker [cholinesterase inhibition] for assessing exposure or outcome related to developmental neurotoxicity."[8]

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[7] Furlong CE. Genetic variability in the cytochrome P450-paraoxonase 1 (PON1) pathway for detoxication of organophosphorus compounds. J Biochem Mol Toxicol. 2007;21(4):197-205. Review. Erratum in: J Biochem Mol Toxicol. 2007;21(5):323.

Furlong CE. Genetic variability in the cytochrome P450-paraoxonase 1 (PON1) pathway for detoxication of organophosphorus compounds. J Biochem Mol Toxicol. 2007;21(5):323.

Furlong CE, Holland N, Richter RJ, Bradman A, Ho A, Eskenazi B. PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. Pharmacogenet Genomics. 2006: 16(3):183-90.

Furlong CE, Cole TB, Jarvik GP, Pettan-Brewer C, Geiss GK, Richter RJ, Shih DM, Tward AD, Lusis AJ, Costa LG. Role of paraoxonase (PON1) status in pesticide sensitivity: genetic and temporal determinants. Neurotoxicology. 2005 Aug;26(4):651-9. Review.

Furlong CE, Cole TB, Walter BJ, Shih DM, Tward A, Lusis AJ, Timchalk C, Richter RJ, Costa LG. Paraoxonase 1 (PON1) status and risk of insecticide exposure. J Biochem Mol Toxicol. 2005;19(3):182-3.

Costa LG, Cole TB, Vitalone A, Furlong CE. Measurement of paraoxonase (PON1) status as a potential biomarker of susceptibility to organophosphate toxicity. Clin Chim Acta. 2005 Feb;352(1-2):37-47. Review.

[8] Slotkin TA, Tate CA, Ryde IT, Levin ED, Seidler FJ. Organophosphate insecticides target the serotonergic system in developing rat brain regions: disparate effects of diazinon and parathion at doses spanning the threshold for cholinesterase inhibition. Environ Health Perspect. 2006 Oct;114(10):1542-6.

Published studies on the toxicity of a related family of pesticides, the organophosphates, have reported that exposures during fetal and newborn life-stages affect diverse cellular functions by mechanisms of toxicity that may be independent of cholinesterase inhibition, or occur at doses at the low end of observable cholinesterase inhibition. This is important because while the systemic toxicity that results from cholinesterase inhibition is reasonably well characterized, it does not explain why rodents exposed pre- and perinatally seem to recover from cholinesterase inhibition relatively rapidly, yet display persistent and more severe damage to the central nervous system.[9] Evidence points to non-cholinergic mechanisms that disrupt multiple distinct brain targets.[10]

EPA recognizes that the database is not adequate to speculate with confidence on what the sensitivity may be at doses below the observable range. Human genetic epidemiology has demonstrated a large range of variability in the human population for PON1 that can exceed 10X (Furlong et al., 2005; Costa et al., 2005). Davies et al. (1996) have reported up to 13-fold variation in PON1 levels in adults. More recently, Furlong et al. (2006) reported a 26-fold variation in sensitivity among newborns to diazinon, a 14-fold variation in sensitivity among mothers, and a 65-fold variation in sensitivity to diazonon between the most sensitive newborn and the least sensitive mother. The same study reported that for chlorpyrifos the sensitivity ranged as high as 164-fold. While carbofuran has not been studied using these protocols, variations in PON1 activity would be expected to impact sensitivity to carbofuran poisoning. Failure to consider this likely scenario is a significant uncertainty biasing the benchmark dose towards the null, i.e. underestimating risk to sensitive populations.

Based on the currently available data, does the panel agree that basing its safety factor on the ratio of BMD_{50} estimates in brain AChE and RBC AChE in juvenile animals is a reasonable approach? Please provide a basis for your conclusion.

The Agency's use of nothing more than a comparative ratio of brain: blood AChE measurements for determination of the FQPA factor is wholly inadequate and unscientific. NRDC recommends that the EPA increase the FQPA factor to reflect uncertainties associated with its failure to test for non-cholinergic toxicity, regional variations in toxicity, impacts from exposure during multiple ages and developmental stages, and possible long-term or permanent cognitive and behavioral impacts. Behavioral and cognitive testing, including learning and memory tests, reflex tests, and others, are key to assessing the true toxic effects of any neurotoxic and fetotoxic chemicals.

[9] Slotkin TA, Cousins MM, Tate CA, Seidler FJ. Persistent cholinergic presynaptic deficits after neonatal chlorpyrifos exposure. Brain Res. 2001 Jun 1;902(2):229-43.

[10] Pope CN. Organophosphorus pesticides: do they all have the same mechanism of toxicity? J Toxicol Environ Health B Crit Rev. 1999 Apr Jun;2(2):161-81. Review.

When reviewing the EPA assessment of a related family of cholinesterase-inhibiting pesticides, the organophosphates, the SAP (2002) raised the concern that, "reliance on a single biochemical assay to measure brain damage may become problematic."[11] This is supported by evidence from rigorous studies of chlorpyrifos that have demonstrated both cholinergic and non-cholinergic toxicity (Slotkin, EHP, 1999; Slotkin et al, Brain Res, 2001; Song et al, Toxicol Appl Pharmacol, 1997). Through the non-cholinergic mechanism, chlorpyrifos elicited widespread neural damage, and disrupted cell development. Through the cholinergic mechanism, chlorpyrifos induced apoptosis during neurulation, resulting in reduced cell numbers in brain regions that are enriched in cholinergic neurons. These regional effects would be undetectable in the toxicology protocols used by the Agency to assess carbofuran. With any developmental neurotoxic chemical such as carbofuran, effects are the result the dose, the duration of the effect, and the stage of development at which the exposure takes place. Exposures during key windows of susceptibility during neural development, even at very low doses, may have permanent, devastating effects on neural function, including behavior and cognition (reviewed in Colborn, EHP, 2006[12]). This was never examined in the current carbofuran assessment, and is a very serious gap in the understanding of the toxic effects of carbofuran.

Point of Departure (PoD) Determination for Dermal Risk Assessment for Workers

In the 2006 and 2007 human health risk assessment for carbofuran, the Agency has relied on oral studies in adult rats for deriving the PoD for dermal risk assessment for workers. The Agency applied a dermal absorption factor of 6% to extrapolate from the oral route to the dermal route. The Agency acknowledges the uncertainties associated with route to route extrapolation.

In 2007, FMC submitted a 21-day dermal rat toxicity study (MRID 47143702) that also included a 7-day range-finding study (MRID 47143701). In these studies, carbofuran at various doses was applied to shaved skin for 6 hours/day, 5 days/week with the skin occluded after application. These studies failed to provide measurements to address time of onset, time of peak, or time to recovery information necessary for the dermal risk assessment. Furthermore, the RBC AChE measurements from both studies were unreliable. The Agency has therefore relied on oral studies for assessing dermal risk of carbofuran to workers.

Do you agree with the Agency's conclusion that the dermal toxicity studies in rats (MRID 47143701-2) are not acceptable for use in extrapolating dermal risk to workers? Please provide a basis for your conclusions.

[11] Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held June 26-27, 2002. Released on July 19, 2002, 26.

[12] Colborn T. A case for revisiting the safety of pesticides: a closer look at neurodevelopment. Environ Health Perspect. 2006 Jan;114(1):10-7. Review.

NRDC disagrees that EPA must use either inadequate data from poorly-conducted studies on rodents, or inappropriate data from an unrelated route of exposure. EPA could and should have required the needed data during the early stages of the reregistration and tolerance reassessment processes. In the absence of reliable data from pre-validated test methods, NRDC recommends that EPA assume 100% dermal absorption.

Since repeatability is one of the most fundamental tenets of the scientific method, the reliance on single studies for route/dose assessment is inadequate as it precludes confirmation of the results. Further, orally ingested residues are subject to digestion and subsequent metabolisms in the liver, while dermally absorbed and inhaled residues do not pass through the digestive tract but instead have direct access to the blood stream and lymphatic circulation. EPA's failure to require robust dermal testing from pre-validated study protocols during the reregistration and tolerance reassessment processes adds an unnecessary uncertainty to the final risk assessment and risk management decisions.

NRDC RECOMMENDS CANCELLING IMPORT TOLERANCES

In July 2006, EPA issued its proposed decision to cancel all domestic uses of the toxic pesticide carbofuran. However, EPA did, inexplicably, choose to retain four import tolerances for coffee, bananas, sugarcane, and rice. While we applauded the decision to cancel carbofuran domestic uses, we petitioned EPA to also revoke all import tolerances.[13] By continuing to allow the import tolerances, EPA is allowing food and products that are contaminated with carbofuran to enter the U.S. without triggering any type of action. Since FDA, and not EPA, checks imports for such violations, only by updating the list of tolerances to reflect risk management decisions correctly can EPA ensure that appropriate action be taken to keep America's food supply safe.

<u>Revoking import tolerances protects both the U.S. population and the international community through PIC reporting requirements</u>

Generally, pesticide manufacturers prefer to voluntarily cancel high risk products, or voluntarily withdraw high risks uses, rather than have EPA issue a ban on those products. This practice highlights a separate, but equally important, reason to revoke tolerances for pesticides that are voluntarily withdrawn or cancelled. When a ban is issued, Prior Informed Consent (PIC) listing is triggered, according to the Rotterdam Convention which entered into force in early 2004.[14] The Convention creates legally binding obligations for the implementation of the Prior Informed Consent (PIC) procedure for pesticides that have been banned or severely restricted for health or environmental reasons. PIC requirements include labelling and obligations to inform other parties of a

[13] Petition to Cancel Carbaryl and Propoxur for Pet Collar Uses; Petition to Revoke All Tolerances of Carbofuran; and Comments on EPA's revised cumulative risk assessment for the N-methyl carbamate pesticides Nov. 26, 2007, EPA-HQ-OPP-2007-0935

[14] Rotterdam Convention http://www.pic.int/home.php?type=t&id=5&sid=16

national ban or restrictions. At this time, there are 24 pesticides subject to PIC procedures.[15]

To avoid PIC listing, that is, to avoid alerting the international community of an unacceptably high risk pesticide, manufacturers will instead issue a quiet voluntary withdrawal, thereby leaving open international markets and trade options. We find this practice morally reprehensible as it results in the transfer of high risk chemicals to the developing countries, where environmental, occupational, and public health protections are generally far weaker than the protections in the U.S. Such countries often rely on the U.S. risk evaluations and risk management decisions as guides and goals in managing their own chemical risks. The U.S. can best serve the international community, and best protect U.S. imports, by making public its risk assessments and risk management determinations, including tolerance revocations.

Failing to revoke import tolerances leads to unacceptable ecological risks

EPA has consistently identified that carbofuran use raises many environmental concerns and acted on that information. In 1992, EPA cancelled the granular formulation with a prolonged phase-out period and in 2002 it also cancelled all liquid formulations because of unacceptably high risks. The 2006 carbofuran Interim Reregistration Eligibility Determination (IRED) concluded that, "based on the assessment of ecological and human health risks associated with carbofuran uses, the Agency has determined that all uses of carbofuran are ineligible for reregistration."[16] The same IRED also concluded that, "carbofuran is very highly toxic to birds on an acute basis, and highly toxic on a sub-acute basis. A chronic effect level could not be established due to the fact that all concentrations tested caused mortality in the test subjects." [17] And, "carbofuran is very highly toxic to freshwater and estuarine/marine fish on an acute basis." [18]

The continuing foreign use of pesticides cancelled in the U.S. presents an unacceptable risk to North American migratory birds wintering in Central and South American countries. Billions of U.S. migratory birds over-winter in countries that currently have registrations for carbofuran, including the major countries listed for importation of coffee, bananas, sugarcane and rice. In fact, carbofuran use on rice was the first major crop use documented to kill birds in significant numbers, and the major reason for cancellation of the granular formulation in 1992. Maintaining a U.S. import tolerance for carbofuran allows Central and South American countries to continue using any formulation of this pesticide on crops for which the U.S. has already determined there are unacceptable risks for protected U.S. migratory birds. EPA must protect U.S. migratory

[15] See Annex III of the Rotterdam Convention for a list of chemicals currently subject to the PIC procedure http://www.pic.int/home.php?type=t&id=29

[16] Carbofuran IRED (2006). http://www.epa.gov/pesticides/reregistration/REDs/carbofuran_ired.pdf

Carbofuran IRED facts. http://www.epa.gov/oppsrrd1/REDs/factsheets/carbofuran_ired_fs.htm

[17] Carbofuran IRED facts. http://www.epa.gov/oppsrrd1/REDs/factsheets/carbofuran_ired_fs.htm

[18] Carbofuran IRED facts. http://www.epa.gov/oppsrrd1/REDs/factsheets/carbofuran_ired_fs.htm

birds on their wintering grounds as well as in the U.S. by cancelling tolerances for these crops. Doing so will encourage the use of legal, safer pesticides and non-chemical practices by foreign growers, at least for those crops that are imported into the U.S.

The ABC "Birds in Agricultural Areas" database contains data from 60 peer reviewed publications documenting the use of U.S. rice fields by 183 species of birds.[19] Thirty-seven of these species are on the ABC-Audubon "Watch List" of vulnerable species, and many are species that migrate to Latin America during the winter season.[20] Agricultural use of carbofuran in Latin America occurs during the rice growing season, which coincides with the seasonal migration pattern of U.S. birds in these countries.

Rice is a very important crop for many shorebirds, waders, waterfowl and some grassland birds; bananas and coffee (especially shade coffee) are also very important winter habitats for many neotropical migrant songbirds. The use of carbofuran in these crops will continue to pose unreasonable risks for U.S. and many additional bird species.

Pursuant to Executive Order 13186 §3(e)(9), EPA must

> identify where unintentional take reasonably attributable to agency actions is having, or is likely to have, a measurable negative effect on migratory bird populations, focusing first on species of concern, priority habitats, and key risk factors. With respect to those actions so identified, the agency shall develop and use principles, standards, and practices that will lessen the amount of unintentional take, developing any such conservation efforts in cooperation with the [US Fish and Wildlife] Service.

Setting an import tolerance for carbofuran constitutes an agency action that is likely to have a measurable negative effect on species of concern as well as other protected species under the Migratory Bird Treaty Act. 16 U.S.C. §§ 703-711. Additionally, since the EPA has already determined in the carbofuran IRED that carbofuran poses an unreasonable risk to protected bird species, the Agency must cancel the import tolerances for rice, bananas, coffee and sugarcane.

Thank you for the opportunity to present comments for your consideration.

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[19] http://www.abcbirds.org/abcprograms/policy/pesticides/biaa/biaa_form2.cfm

[20] http://web1.audubon.org/science/species/watchlist/browsewatchlist.php