November 20, 2006

DOCKET ID No. EPA-HQ-OPP-2005-0162

Re: EPA's Interim Reregistration Eligibility Decision (IRED) for carbofuran (OPP-2005-0162-0307)

These comments are supported by:

Natural Resources Defense Council, Jennifer Sass, Ph.D.
Pesticide Action Network North America, Susan Kegley, Ph.D.
Defenders of Wildlife, Caroline Kennedy
The Endocrine Disruption Exchange (TEDX), Theo Colborn, Ph.D.
Center for Environmental Health, Caroline Cox, Ph.D.
Steve Sheffield, Ph.D.
Northwest Coalition for Alternatives to Pesticides, Aimee Code
Rachel Carson Council, Inc., Diana Post
Beyond Pesticides, John Kepner
American Bird Conservancy, Michael Fry, Ph.D.

Our organizations collectively represent millions of Americans that support protection of public health, worker safety, and environmental stewardship. On behalf of our members and supporters, we submit the following comments.

We strongly support the EPA finding that carbofuran is not eligible for reregistration. We urges the EPA to immediately suspend all uses of carbofuran, rather than allowing limited uses to continue on some crops, and allowing prolonged phase-out period that continues to pose unacceptably high risks to humans and ecosystems. Continued use of carbofuran is unjustified.

Information and documentation of the EPA review of carbofuran can be found at: http://www.epa.gov/oppsrrd1/reregistration/carbofuran/

Carbofuran is a significant risk to human and ecological health

NRDC submitted comments during Phase 5 (May 22, 2006; EPA-HQ-OPP-2005-0162) on the HED Revised Risk Assessment for the Reregistration Eligibility Decision (RED) Document (Phase 4). These comments are incorporated by reference. EPA responded to the comments by NRDC (July 19, 2006; EPA-HQ-OPP-2005-0162-0310) as well as the comments submitted by the registrant (July 21, 2006; EPA-HQ-OPP-2005-0162-0309). At that time, EPA's own analysis of carbofuran concluded that it poses significant human health risks through food, drinking water, and occupational exposure, and poses significant risks for wildlife and aquatic life. In light of the health risks to the general population, to children, and to workers, and given the availability of less toxic alternatives, NRDC asserted that the registrant could not meet its burden of showing that the pesticide does not pose an unreasonable risk of adverse effects, when considering the risks and benefits of its use.

EPA decision to cancel carbofuran is widely supported

Because of these and other concerns, on August 3, 2006, EPA announced its intention to cancel all uses of carbofuran and to revoke the associated tolerances (legal residue limits on food).[1] The pesticide, which is sold under the name "Furadan" by FMC Corporation, is one of the most toxic pesticides on the market. The cancellation is immediately effective for the main uses of carbofuran: alfalfa, corn, cotton, cotton, potatoes, and rice. Its use will be phased out over four years for other minor uses including artichokes, chili peppers in the southwest, cucumbers, spinach for seed, sunflowers, and pine seedlings. The cancellation also applies to use on most major imported agricultural products, meaning that countries wishing to export agricultural produce to the United States will not be able to use carbofuran on those crops.

The announcement to cancel carbofuran was widely supported by environmental and public health groups, including: American Bird Conservancy, Alaska Bird Observatory, Archbold Biological Station, Beyond Pesticides, Bird Conservation Network, Center for Biological Diversity, Defenders of Wildlife, Endangered Habitats League, Friends of Dyke Marsh, Hampshire Bird Club, Massachusetts Audubon Society, Minnesota River Valley Audubon Chapter, National Audubon Society, Natural Resources Defense Council, Northwest Coalition for Alternatives to Pesticides, Pesticide Action Network North America, Riveredge Bird Club, Seattle Audubon Society, Taku Conservation Society, Tennessee Ornithological Society, The Endocrine Disruption Exchange, The Institute for Bird Populations, Virginia Society of Ornithology, Washington Toxics

[1] U.S. Continues to Set Bar on Pesticide Safety. EPA newsroom. Washington, D.C. - Aug. 3, 2006.
http://yosemite.epa.gov/opa/admpress.nsf/e987e762f557727d852570bc0042cc90/1cbb1b3bd0c3947f852571bf0066fbf7!OpenDocument

Coalition, Wildlife Center of Virginia, Wisconsin Society for Ornithology, World Wildlife Fund, Xerces Society, Maryland Ornithological Society.[2]

Summary of EPA assessment

An FQPA factor of 5X, along with an intraspecies factor of 10X and interspecies factor of 10X was applied to the pup BMDL10 (0.03 mg/kg; brain ChE inhibition) and results in an acute PAD of 0.00006 mg/kg/day (0.06 μg/kg/day) for the general population and all population subgroups. EPA has classified carbofuran as "not likely" a human carcinogen.

NRDC continues to disagree with EPA that a 5X uncertainty factor "adequately addresses 'juvenile sensitivity' and uncertainty regarding the available database" (EPA to NRDC at 4). As detailed below, age-related sensitivity for brain ChE activity is reported to be 5-fold. However, this fails to capture the most sensitive measurement, which is RBC (not brain) ChE activity. This also fails to capture significant database uncertainties. And, finally, this fails to adjust for significant database gaps where no data is available.

Age-related sensitivity is 5-fold in DNT study

EPA has applied an FQPA Safety Factor of 5X, quantitatively derived from studies comparing brain cholinesterase inhibition in the male rat pup with the adult rat (EPA response to NRDC at 4)[3]. EPA is correct that an FQPA of at least 5X is supported by the rat developmental neurotoxicity (DNT) study indicating that juveniles are 5X more sensitive than adults (revised RA at 5), and the brain comparative ChE study indicating that PND11 pups are 2.5X more sensitive than adults (revised RA at 4; IRED at 6). EPA also acknowledges that the rat multi-generation reproduction study, both provide "evidence of qualitative increased susceptibility" (IRED at 6). EPA failed to adjust for significant qualitative differences in age-related susceptibility.

Most sensitive endpoint likely to be age-related RBC ChE activity, for which registrant failed to provide reliable data in pups

In addition to accounting for a 5-fold observed juvenile sensitivity from the DNT study, EPA claims that the 5X FQPA is also meant to adjust for the observed 5-fold difference between brain ChE inhibition and RBC ChE inhibition in adult rats. The comparative ChE rat study only reported on brain ChE, whereas RBC ChE is the more sensitive endpoint for carbofuran toxicity (IRED at7). Unfortunately, EPA does not have data on carbofuran-dosed RBC ChE activity in juvenile animals. EPA assumed, without evidence, that because data from adult rats indicate a 5-fold increased sensitivity in RBC compared with brain ChE, the same magnitude of sensitivity difference would hold true for juvenile. However, EPA provided no data to support this assumption. Moreover, this ignores the real purpose of the FQPA, which is not to adjust for differences between brain and RBC responses,

[2] Pesticide Ban Follows Millions of Bird Deaths. American Bird Conservancy and Defenders of Wildlife Press Release. Washington, D.C. 3:00 p.m. 3 August, 2006.

[3] EPA response to NRDC. July 19, 2006; EPA-HQ-OPP-2005-0162-0310

but rather is meant to adjust for differences between adult and juvenile responses. That is, the central question is not the sensitivity of adult RBC v. adult brain ChE, but rather the sensitivity of adult RBC v. juvenile RBC ChE. Since EPA provided no data on juvenile RBC ChE activity, and since EPA acknowledges that RBC ChE is more sensitive than brain ChE, the impact of carbofuran on juvenile v. adult RBC ChE activity remains a significant uncertainty. EPA should support its selection of an FQPA factor, or select the default factor of 10X.

EPA identified uncertainties with available data, but did not apply the database uncertainty factor

EPA further claims that the same 5X FQPA factor, already used twice, is also meant to adjust for outstanding database uncertainties (IRED at 6). The EPA notes that all the registrant studies used to inform the FQPA are limited. EPA provides no data to support the magnitude of uncertainty, or the bounds of that estimate. This could be done by providing a statistical analysis of the ability of the scientific studies to detect an effect (a power calculation), and a statistical uncertainty analysis. This was not done. A more appropriate uncertainty factor may be 5X or 50X or 500X, or more. EPA should support its selection of a database uncertainty factor, or select the default factor of 10X.

EPA failed to adjust for lack of critical data

In addition to significant uncertainties in the data provided by the registrant to the EPA, there are significant gaps in the database. EPA identified the following studies that are "not available" (HED at Table 4):[4]

- 90-day oral toxicity rodents
- 90-day oral toxicity non-rodents
- 90-day dermal toxicity
- 90-day inhalation toxicity
- acute neurotoxicity screening battery

EPA identified the following studies that are still needed (HED at 63, 64): [5]

- product chemistry: storage stability data
- residue chemistry
- 28-day inhalation study in rats
- comparative cholinesterase data on RBC and brain ChE inhibition in pups and adults

These are significant data gaps, and leave the carbofuran assessment with considerable uncertainty. For example, EPA has identified a lack of inhalation studies and of acute neurotoxicity studies. The failure of the registrant to provide these data in a timely manner leaves EPA hamstrung in its ability to provide a rigorous scientific review, and unfairly benefits the registrant by treating no data as neutral, whereas data would likely demonstrate significant hazards associated

[4] Table 4, HQ-OPP-2005-0162-0307 HED assessment, July 2006

[5] Table 4, HQ-OPP-2005-0162-0307 HED assessment, July 2006

with carbofuran exposure. EPA has not applied an uncertainty factor for these critical database gaps. How and when does EPA intend to acquire these data?

Food and water exposure data are likely underestimates

EPA finds that the estimated acute dietary (food only) exposure exceeds the EPA level of concern for the US population and all reported population subgroups, including children, at the 99.9 percentile. Carbofuran dietary exposure at the 99.9th percentile was estimated at 260% of the aPAD (0.000154 mg/kg/day) for the US population and 490% of the aPAD for children 1-2 yrs old (IRED at 9, 10). However, HED noted that the USDA pesticide data program (PDP) underestimated residues on bananas and grapes (HED at 38). How many other foods, especially those commonly consumed by kids, are also underestimated in the PDP database? EPA has not applied an uncertainty factor for these underestimates or uncertainties in the available database.

Water consumption alone also exceeds the Agency's LOC. EPA reports that targeted monitoring of water in areas of carbofuran use report peak carbofuran concentrations ranging from 1.4-176 ppb, whereas non-targeted monitoring tends to show detections that rarely exceed 1 ppb (IRED at 11). These data demonstrate the need for targeted monitoring to support EPA assessments that reflect the exposure of vulnerable populations. Conventional water treatment does not remove carbofuran (IRED at 12). Moreover, PDP data are generally from deep ground water or surface water systems and do not include private wells. These PDP database estimates are likely to underestimate exposures to people that drink water from shallow private wells in areas of high carbofuran use (IRED at 12). EPA has not applied an uncertainty factor for these underestimates or uncertainties in the available database.

The dermal penetration study may underestimate exposure

The dermal penetration study used by EPA was a 24-hr duration study (Shah et al, 1987). EPA used this study to derive a dermal absorption factor of 6% (IRED at 13) to calculate occupational exposure and risks. This study, almost 20 years old, did not demonstrate that skin loadings were appropriately low. The HSRB rejected and discredited dermal absorption studies where the chemical loadings on small areas of skin were so high that the absorption potential was significantly reduced (HSRB report at 61, April, 2006[6]). This study may significantly underestimate carbofuran penetration, and therefore underestimate exposure. EPA should either provide detailed evidence that the study was well-conducted and appropriate skin loadings were tested, or assume 100% dermal penetrance, to be protective, rather than rely on weak data.

Data suggest effects at low doses below significant ChE inhibition

EPA used the rat comparative ChE study for risk assessment (BMDL10=0.03 mg/kg/day, based on brain ChEi of PND11 male rats; IRED at 8). However, EPA reported that the comparative ChE study showed dose-related decrease in

[6] http://www.epa.gov/osa/hsrb/files/april2006mtgfinalreport62606.pdf

motor activity in the juvenile rats at all doses tested, and therefore did not identify a NOAEL (HED at 27-28). The decreased motor activity coincided with decreased RBC and brain ChE inhibition, particularly at the low end of the dose-response curve (HED at 28). This is evidence of effects in developing rodents at doses below those that cause measurable (albeit non-statistical) cholinesterase inhibition, and may be through non-cholinergic mechanisms (see review by T Colborn, Env Health Perspect, Jan 2006). EPA has not accounted for the potential for low-dose toxicity.

Recent published data highlights carbofuran risks to human health, and need to account for non-cholinergic mechanisms of toxicity

Recent research implicates carbofuran in risk of diabetes during pregnancy. In 2006, NIH researchers reported a significant increase in risk of gestational diabetes mellitus (GDM) among women who reported exposure during pregnancy to carbofuran (Total N=11,273; 4.5% reported having GDM).[7] The same disease was also associated with two other insecticides (diazinon, phorate) and five herbicides (2,4,5-T, 2,4,5-TP, atrazine, butylate, EPTC). Women who mixed or applied pesticides or repaired pesticide related equipment during pregnancy (agricultural exposure) had a two-fold increased risk of developing GDM [odds ratio (OR = 2.2; 95% confidence interval (CI): 1.5–3.3)]. It has been medically established that mothers with GDM have a higher risk of hypertension, preeclampsia, urinary tract infections, cesarean section, and future diabetes. Infants of gestational diabetic pregnancies have an increased risk of neural tube defects, neonatal low sugar, low calcium, low magnesium, high liver enzymes, and subsequent childhood and adolescent obesity.

Recent research provides more evidence of non-cholinergic toxic mechanisms of carbofuran. In 2006, researchers in India reported significant neurotoxic effects of carbofuran through a mechanism of oxidative stress.[8] Specifically, carbofuran exposure induced lipid peroxidation, with concomitant reduction in the activity of enzymes that would otherwise protect the system from oxidative stress, including superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase. Impaired motor function was also reported, along with cognitive deficits measured by avoidance responses. The EPA assessment of carbofuran has not considered or adjusted for the effects of non-cholinesterase mechanisms of toxicity.

Failing to account for non-cholinergic toxicity may be a significant oversight, considering another recent publication that compared the effects of acute versus chronic exposure to carbofuran.[9] Using biochemical techniques,

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[7] Saldana TM et al. Pesticide Use And Gestational Diabetes Mellitus Among Wives Of Farmers In The Agricultural Health Study. Am J Epidemiol 2006 Jun;163(11 Suppl):S77

[8] Kamboj A et al. Carbofuran-induced neurochemical and neurobehavioral alterations in rats: attenuation by N-acetylcysteine. Exp Brain Res. 2006, Apr; 170(4):567-75

[9] Kaur M and Sandhir R. Comparative effects of acute and chronic carbofuran exposure on oxidative stress and drug-metabolizing enzymes in liver. Drug Chem Toxicol. 2006; 29(4):415-21

researchers from India reported that cholinesterase activity, the hallmark of carbofuran exposure, is more sensitive to acute exposures than chronic exposures. However, lipid peroxidation, a direct measurement of cellular damage, was more sensitive to chronic exposures than acute ones. These data suggest that acute toxicity tests of carbofuran, such as those used by EPA, are likely to fail to detect the harm from chronic exposure to carbofuran. Carbofuran is a relatively stable pesticide in aquatic environments, and is detected in water (see USGS data[10]), fruits, and vegetables, making chronic exposure likely for aquatic populations and human ones.

Conclusion

We strongly supports the EPA finding that carbofuran is not eligible for reregistration. We urges the EPA to immediately suspend all uses of carbofuran, rather than allowing limited uses to continue on some crops, and allowing prolonged phase-out period that continues to pose unacceptably high risks to humans and ecosystems. Continued use of carbofuran is unjustified.

Respectfully,
Jennifer Sass, Ph.D.
Natural Resources Defense Council
Washington, DC, 20005
email: jsass@nrdc.org

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)

[10] USGS reports that at the 95th percentile, carbofuran detections were 0.048 µg/L in surface streams. Summary of Results of the National Water Quality Assessment Program (NAWQA), 1991-2001. http://ca.water.usgs.gov/pnsp/pestsw/Pest-SW_2001_table1_ag.html