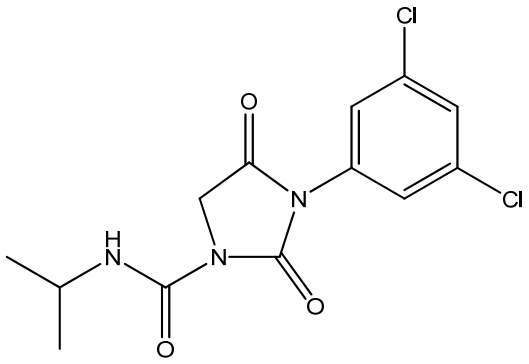
Iprodione [CASRN: 36734-19-7]

Materials for the July 28-29, 2009 Meeting of the California Environmental Contaminant Biomonitoring Program (CECBP) Scientific Guidance Panel (SGP)

Agenda Item: "Potential Designated Chemicals: Pesticides"



Exposure or potential exposure to the public or specific subgroups:

Iprodione is a dicarboximide fungicide that is widely used in California on a variety of agricultural crops, for landscape maintenance, and on ornamental plants. The California Department of Pesticide Regulation (CDPR) reported that 251,168 pounds of iprodione were applied in 2007 (CDPR, 2007). Total pounds applied in California for each of the last five years and pounds applied on specific crops are shown in the table below. CDPR (2007) notes that year-to-year variations in pounds applied may be affected by a variety of factors including weather conditions, pest pressures, and planted acreage.

Pounds iprodione applied in California (CDPR, 2003-2007)

	2003	**2004**	**2005**	**2006**	**2007**
Total pounds applied	**287,850**	**261,218**	**284,984**	**301,231**	**251,168**
Almond	117,499	111,318	124,582	135,509	117,.099
Carrot	17,870	18,865	20,676	18,278	21,219
Lettuce, head	33,416	34,734	30,492	28,276	23,390
Lettuce, leaf	23,439	26,844	25,073	24,639	16,460
Peach	16,431	14,138	12,873	14,146	11,012

CDPR (2009) has found iprodione residues on samples of raw agricultural commodities in their Residue Monitoring Program. Iprodione had been used in residential settings, but that use was cancelled when the fungicide was re-registered in 1998, due to cancer risk concerns (U.S. EPA, 1998a).

Known or suspected health effects:

Iprodione is listed under Proposition 65 as known to cause cancer. It is similar in structure to two other fungicides on the Proposition 65 list: procymidone (cancer) and vinclozolin (cancer and developmental toxicity). Iprodione is an anti-androgen (U.S. EPA, 1998b; Blystone et al.,

2007; Blystone et al., 2009). A recent study found that iprodione lowers serum testosterone levels, inhibits testicular testosterone biosynthesis and delays pubertal development in male rats (Blystone et al., 2007). The European Union has classified the endocrine disruption potential of iprodione as Category 2, substances for which *in vitro* data indicate potential for endocrine disruption in intact animals (DHI, 2007).

The principal breakdown product of iprodione is 3,5-dichloroaniline (3,5-DCA). Few toxicology studies were identified for 3,5-DCA. Lo et al. (1990) found that 3,5-DCA is the most nephrotoxic of the dichloroanilines studied and that it can cause acute kidney toxicity in rats. U.S. EPA (1998b) treats 3,5-DCA as a cancer-causing chemical based on the carcinogenicity of the structurally related compound p-chloroaniline, which is listed as known to cause cancer under Proposition 65.

Potential to biomonitor:

Physical and chemical properties (SRC, 2009):

Iprodione
Molecular weight: 330.17
Vapor pressure: 3.75×10^{-9} mm Hg
Water solubility: 13.9 mg/L at 25ºC
Octanol/water partition coefficient: Log $K_{ow} = 3.0$

3,5-Dichloroaniline (3,5-DCA)
Molecular weight: 162.02
Vapor pressure: 2.12×10^{-2} mm Hg
Water solubility: 784 mg/L
Octanol/water partition coefficient: Log $K_{ow} = 2.9$

Pharmacokinetics and metabolism: Iprodione is well absorbed orally. Studies in animals found that urine was the primary route of elimination following repeated low doses of iprodione and that iprodione is mostly excreted within the first 24 hours (U.S. EPA, 1998b). Analyzing human metabolism and excretion in two human subjects, Lindh et al. (2007) found that iprodione was rapidly metabolized to 3,5-DCA and mostly excreted in urine during the first 24 hours.

Persistence: Iprodione is degraded in the environment by both hydrolysis (half-life at pH 7, 4.7 days and at pH 9, 27 minutes) and by microbial degradation (U.S. EPA, 1998a). Degradation in soils at or above pH 7 would be expected to be more rapid than in acidic soils. Iprodione is rapidly metabolized in plants to 3,5-DCA (HSDB) and is also converted to 3,5-DCA through microbial degradation (HSDB; Athiel et al., 1995). The estimated half-life of 3,5-DCA in sediment is 340 days (PBT Profiler).

Bioaccumulation: Iprodione BCF = 41; 3,5-DCA BCF = 34 (both estimated using PBT Profiler)

Past biomonitoring studies: Turci et al. (2006) analyzed urine samples from 153 non-occupationally exposed individuals in rural central Italy and found 3,5-DCA in 151of 153

samples. Levels ranged from 0.02-6.7 µg/L, with a mean of 0.63±1.01 µg/L and a median value of 0.26 µg/L. Lindh et al. (2007) analyzed urine from two individuals (one male and one female) for iprodione, as part of a Swedish study to develop analytical methods. Levels of 3,5-DCA were 0.4 µg/L and 5 µg/L, for the male and female subject, respectively.

Exposure to 3,5-DCA may also occur as a result of its use as a chemical intermediate (to produce, for example, agricultural chemicals, pigments and dyes). It is also a metabolite of the fungicides vinclozolin and procymidone. A study in Italy found 3,5-DCA in some commercial composts (Vanni et al., 2000).

Need to assess efficacy of public health actions:

Exposure to iprodione potentially poses serious health concerns, including cancer and hormone disruption. Available biomonitoring studies in Europe have found the iprodione metabolite 3,5-DCA in non-occupationally exposed individuals; in California, the CDPR has found iprodione residues in numerous produce samples. Biomonitoring iprodione will help the State to assess the extent of exposure to California residents.

Availability of analytical methods: GC/MS-SIM and LC/MS-MS methods for analyzing 3,5-DCA have been developed (Lindh et al., 2007; Turci et al., 2006).

Availability of adequate biospecimens: Urine.

Incremental analytical cost: Analysis could be bundled with diuron and other chemicals with dichloroaniline metabolites (e.g., propanil, triclocarban).

References:

Athiel P, Alfizar, Mercadier C et al. (1995). Degradation of iprodione by a soil *arthrobacter*-like strain. *Appl Environ Microbiol* 61:3216-3220.

Blystone CR, Lambright CS, Cardon MC, et al. (2009). Cumulative and antagonistic effects of a mixture of the antiandrogens vinclozolin and iprodione in the pubertal male rat. *Toxicol Sci* [epub ahead of print] June 29, 2009.

Blystone CR, Lambright CS, Furr J et al. (2007). Iprodione delays male rat pubertal development, reduces serum testosterone levels, and decreases ex vivo testicular testosterone production. *Toxicol Lett* 174:74-81.

California Department of Pesticide Regulation (CDPR, 2007). *Summary of Pesticide Use Report Data.* 2007. *Indexed by Chemical.* Available at: http://www.cdpr.ca.gov/docs/pur/pur07rep/chmrpt07.pdf

California Department of Pesticide Regulation (CDPR, 2003-2007). *Summary of Pesticide Use Report Data. Pesticide Use Annual Summaries* for the years 2003, 2004, 2005, 2006, 2007. *Summary Report Indexed by Chemical.* Available at: http://www.cdpr.ca.gov/docs/pur/purmain.htm

California Department of Pesticide Regulation (CDPR, 2009). *Residue Monitoring Program. Summaries of DPR report residues in fresh produce. 2008.* Available at: http://www.cdpr.ca.gov/docs/enforce/residue/rsmonmnu.htm

DHI Water and Environment (DHI, 2007). Study on enhancing the endocrine disruptor priority list with a focus on low production volume chemicals. Revised Report to DG Environment. ENV.D.4/ETU/2005/0028r. May 2007. Available at: http://ec.europa.eu/environment/endocrine/documents/final_report_2007.pdf

HSDB (Hazardous Substances Data Bank). Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

Lindh CH, Littorin M, Amilon A, et al. (2007). Analysis of 3,5-dichloroaniline as a biomarker of vinclozolin and iprodione in human urine using liquid chromatography/triple quadrupole mass spectrometry. *Rapid Commun Mass Spectrom* 21:536-542.

Lo HH, Brown PI, Rankin GO (1990). Acute nephrotoxicity induced by isomeric dichloroanilines in Fisher 344 rats. *Toxicology* 63: 215-279.

PBT Profiler. Developed by Environmental Science Center for the Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. Available at: http://www.pbtprofiler.net.

Syracuse Research Corporation (SRC, 2009). PhysProp Database. Available at: http://www.cdpr.ca.gov/docs/pur/pur07rep/chmrpt07.pdf

Turci R, Barisano A, Balducci C et al. (2006). Determination of dichloroanilines in human urine by gas chromatography/mass spectrometry: validation protocol and establishment of Reference Values in a population group living in central Italy. *Rapid Commun Mass Spectrom* 20:2621-2625.

U.S. Environmental Protection Agency (U.S. EPA, 1998a). R.E.D. Facts. Iprodione. Prevention, Pesticides and Toxic Substances. EPA-738-F-98-017. November 1998.

U.S. Environmental Protection Agency (U.S. EPA, 1998b). Reregistration Eligibility Decision (RED) Iprodione. Prevention, Pesticides and Toxic Substances. EPA738-R -98-019. November 1998.

Vanni A, Gamberini R, Calabria A et al. (2000). Determination of presence of fungicides by their common metabolite, 3,5-DCA, in compost. *Chemosphere* 41:453-458.