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SUBJECT: CANCER POTENCY ESTIMATE FOR CHLOROTHALONIL

On February 12, 2018, the Environmental Monitoring Branch requested that the Human Health Assessment (HHA) Branch provide a cancer potency value to calculate a cancer risk estimate for chlorothalonil. Chlorothalonil is included in DPR's Air Monitoring Network (AMN) and has been detected at quantifiable concentrations in California in the last three years.

HHA prioritized chlorothalonil for comprehensive risk assessment to update the January 2005 risk characterization document that focused on dietary exposure. The expanded scope of the risk analysis includes both occupational and bystander exposures. The Risk Assessment Section (RAS) in HHA revised the hazard identification and proposes a cancer potency estimate of 0.016 $(mg/kg/day)^{-1}$ which utilized a multi-tumor analysis approach based on the combined incidence of kidney and forestomach tumors in rats from a 2-year carcinogenicity study (Wilson and Killeen 1989).

Recommendation:

A human equivalent cancer potency value (q^*) for chlorothalonil of 0.016 $(mg/kg/day)^{-1}$ is recommended for estimating cancer risks from airborne chlorothalonil.

Background:

In 2005, HHA (formerly the Medical Toxicology Branch) finalized a RCD for dietary exposures for chlorothalonil (Lim 2005). The original cancer potency value of 0.011 $(mg/kg/day)^{-1}$ was estimated for chlorothalonil based on the combined incidence of kidney tumors from two separate rat studies from the same investigator using the same strain of rats (Wilson *et al.* 1985; Wilson and Killeen 1989).

RAS has revised the cancer potency value for several reasons: 1) The two carcinogenicity studies in rats were conducted several years apart, so the data should be considered separately (Wilson *et*

al. 1985; Wilson and Killeen 1989); 2) The study body weight (as a time-weighted average) should be used instead of a default body weight since there are large differences between the male and female body weights; and, 3) The assessment should also consider the overall tumor response in each experiment by counting animals with either kidney or forestomach tumors or both based on USEPA's cancer guidelines (US EPA 2005).

The Office of Health Hazard Assessment (OEHHA) calculated a cancer potency estimate of 0.017 $(mg/kg/day)^{-1}$ for chlorothalonil for Proposition 65 listing using the same data and a similar multi-tumor analysis approach (OEHHA 2011). Rather than adopting OEHHA's cancer potency value for chlorothalonil, RAS chose to do a multi-tumor analysis using the Multi-Tumor program in US EPA's Benchmark Dose Software (BMDS) since BMDS is publicly available and, therefore, the calculation is more transparent.

Summary of Toxicology:

Tables 1 and 2 summarize the kidney and forestomach tumor incidence from Wilson *et al.* (1985) and Wilson and Killeen (1989), respectively. Table 3 summarizes the cancer potency estimates based on the kidney and forestomach tumor incidences, both separately and combined.

Table 1. Neoplastic Kidney and Forestomach Lesions in Rats after Lifetime Dietary Exposure to Chlorothalonil[a]

Effects	Dose (mg/kg/day)			
	0	40	80	175
MALES				
Kidneys				
Tubular adenoma	0/60^{++}	3/60	5/58*	7/60**
Tubular carcinoma	0/60^{+++}	4/60	2/58	13/60***
Combined	0/60^{+++}	7/60**	7/58**	18/60***
Forestomach				
Papilloma and carcinoma	0/60^{+}	1/60	1/58	3/60
FEMALES				
Kidneys				
Tubular adenoma	0/60^{+++}	3/60	10/59***	15/60***
Tubular carcinoma	0/60^{+++}	1/60	0/59	11/60***
Combined	0/60^{+++}	4/60	10/59***	23/60***
Forestomach				
Papilloma and carcinoma	0/60^{+++}	1/60	2/59	7/60**

a Data from Wilson *et al.* (1985) and reevaluation of pathology from Wilson *et al.* (1986). Incidences were expressed as the number of animals bearing tumors. All animals examined were considered at risk, except for those which died before day 365 of the study. The first tumors were diagnosed on day 417 (kidney) and on day 632 (forestomach).

*,**,*** Significantly different from controls at $p < 0.05$, 0.01, and 0.001, respectively, based on the Fisher's exact test.

$^{+}$,$^{++}$,$^{+++}$ Significant trend at $p < 0.05$, 0.01, and 0.001, respectively, based on the Cochran-Armitage Trend Test.

Table 2. Neoplastic Lesions of the Kidney and Forestomach in Rats after Chronic Exposure to Chlorothalonil in the Diet[a]

Effects	Dose (mg/kg/day)				
	0	2	4	16	182
MALES					
Kidneys					
Tubular adenoma	$1/55^{+++}$	1/54	1/54	3/54	17/55***
Tubular carcinoma	$0/55^{+++}$	0/54	0/54	1/54	7/55**
Combined[b]	$1/55^{+++}$	1/54	1/54	4/54	23/55***
Forestomach					
Papilloma	$0/55^{++}$	0/54	3/54	2/54	5/55*
FEMALES					
Kidneys					
Tubular adenoma	$0/55^{+++}$	0/54	0/55	0/53	24/55***
Tubular carcinoma	$0/55^{+++}$	0/54	0/55	0/53	11/55***
Combined	$0/55^{+++}$	0/54	0/55	0/53	32/55***
Forestomach					
Papilloma and/or carcinoma	$1/55^{+++}$	1/54	2/55	5/53	9/55**

a Data from Wilson and Killeen (1989). Incidences were expressed as the number of animals bearing tumors (with % incidence in parenthesis). All animals examined were considered at risk, except for those which died before day 365 of the study. The first tumors were diagnosed on days 497 (kidney) and on day 525 (forestomach).

b Rats with either adenoma or carcinoma only, or both.

*,**,*** Significantly different from controls at $p < 0.05$, 0.01, and 0.001, respectively, based on the Fisher's exact test.

$^{++}$,$^{+++}$ Significant trend at $p < 0.01$ and 0.001, respectively, based on the Cochran-Armitage Trend Test.

Table 3. Cancer Potency Estimates for Rats Exposed to Chlorothalonil in the Diet for a Lifetime[a]

Studies	Sex, strain, species, body weight	Type of neoplasm	Animal cancer potency ($mg/kg/day^{-1}$)[a]		Human cancer potency ($mg/kg/day^{-1}$)[b]	
			MLE	95% UB	MLE	95% UB
Wilson *et al.* 1985	Male F344/N Rats (0.383kg)	Renal tubular epithelial adenoma or carcinoma	0.00197	0.00260	0.007	0.010
		Forestomach papilloma or carcinoma	0.00028	0.00059	0.001	0.002
		Multisite	0.00224	0.00291	0.008	0.011
	Female F344/N Rats (0.240kg)	Renal tubular epithelial adenoma or carcinoma	0.00189	0.00292	0.008	0.012
		Forestomach papilloma or carcinoma	0.00063	0.00087	0.003	0.004
		Multisite	0.00221	0.00343	0.009	0.014
Wilson and Killeen 1989	**Male F344/N Rats (0.390kg)**	Renal tubular epithelial adenoma or carcinoma	0.00279	0.00387	0.010	0.014
		Forestomach papilloma or carcinoma	0.00043	0.00094	0.002	0.003
		Multisite	**0.00322**	**0.00438**	**0.012**	**0.016**
	Female F344/N Rats (0.240kg)	Renal tubular epithelial adenoma or carcinoma	0.00157	0.00208	0.006	0.009
		Forestomach papilloma or carcinoma	0.00085	0.00153	0.004	0.006
		Multisite	0.00205	0.00279	0.008	0.012

a Maximum likelihood estimate (MLE) / 95 percent upper bound estimate (95% UB).
b Human cancer slope factors were calculated using time-weighted average rat body weights for the control groups and default human body weight of 70 kg. Human cancer slope factor= rat cancer slope factor x (human body weight/rat body weight)$^{1/4}$. Shown for both MLE and 95% UB.
c After adjusting for oral absorption (34%), the human cancer potency was estimated to be 0.034 (MLE) and 0.047 (95% UB) $(mg/kg/day)^{-1}$.

References

Lim, L.O., 2005. Chlorothalonil Risk Characterization Document for Dietary Exposure. RCD 2006-02. Department of Pesticide Regulation, California Environmental Protection Agency. Sacramento, CA. January 5, 2005.

OEHHA, 2011. No Significant Risk Level (NSRL) for the Proposition 65 Carcinogen Chlorothalonil. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Sacramento, CA. March 2011. (http://oehha.ca.gov/prop65/law/pdf_zip/031811chlorothalonilNSRL.pdf)

US EPA, 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/-11F. Risk Assessment Forum, U.S. Environmental Protection Agency. Washington, D.C. March 2005.

Wilson, N.H., and J.C. Killeen, 1989. A tumorigenicity study of technical chlorothalonil in rats. Ricerca, Inc. . DPR Vol. 275-164, Rec. No. 74770.

Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, 1985. A tumorigenicity study of technical chlorothalonil in rats. SDS Biotech Corp. DPR Vol. 275-100 to 104, Rec. No. 34366, 34367, 34348-34352, and 34372.

Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, 1986. Histopathological reevaluation of renal tissue from a rat tumorigenicity study with chlorothalonil. SDS Biotech Corp. DPR Vol. 275-131, Rec. No. 50897.