This is the Final Statement of Reasons for a specific regulatory level for chlorothalonil, a chemical listed as known to the State to cause cancer under Proposition 65. On March 18, 2011, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt a No Significant Risk Level (NSRL) for chlorothalonil in Title 27, California Code of Regulations, section 25705(b). The Initial Statement of Reasons set forth the grounds for the proposed amendment. The Initial Statement of Reasons included a technical support document that laid out the scientific basis for the proposed NSRL. These documents are available at: http://www.oehha.ca.gov/prop65/law/031811nsrl.html. A public comment period was provided from March 18 until May 2, 2011 and later extended to June 2, 2011, based on a request from an interested party. The Notice of Proposed Rulemaking stated that a public hearing would be held only on request; no such request was received. OEHHA received one set of written public comments on June 2, 2011.

On April 7, 2011, OEHHA provided the technical support document forming the basis for the proposed regulatory level for chlorothalonil to the members of the Carcinogen Identification Committee for their review and comment as required by Section 25302(e). No comments were received from any committee members.

During the pendency of this regulatory action, an amendment to Section 25703, which describes the methodology to be used in calculating an NSRL was finalized (Section 25703(a)(6)). The amendment states that when converting estimates of a chemical’s animal cancer potency to estimates of human cancer potency, the animal potency shall be multiplied by the ratio of human to animal body weights raised to the one-fourth power, rather than to the one-third power as in the past. On January 13, 2012, a notice was filed to amend the proposed chlorothalonil regulation and modify the technical support document to apply the new scaling factor, which increased the value of the NSRL for chlorothalonil from 27 micrograms per day to 41 micrograms per day. The

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1 The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code, section 25249.5 et seq., commonly known as Proposition 65, hereafter referred to as “Proposition 65” or “The Act”.
2 All further section references are to sections of Title 27 of the California Code of Regulations, unless otherwise noted.
public comment period on the modified regulation ended on January 30, 2012. One letter was received on the modified text of the regulation, from the same individual who commented on the original version of the proposed regulation. The letter requested that the comments previously submitted “should be considered by OEHHA as originally submitted.” Responses to the original comments are included below. The letter provided no substantive comments on the modified regulation. OEHHA therefore made no change to the regulation.

The modified proposed regulation and updated technical support document was provided to the Carcinogen Identification Committee members on January 13, 2012. No comments were received from any committee members.

**SUMMARY AND RESPONSE TO COMMENTS RECEIVED**

One set of written comments was received during the March 18 – June 2, 2011, public comment period from Debbie Stubbs of GB Biosciences Corporation, a member of the Syngenta Group, and Syngenta Crop Protection LLC. Below the comments are summarized or quoted and responses to them are provided.

**Comment 1:**
“Forestomach tumors in rodents are considered not relevant for human risk assessment based on the lack of an anatomically similar organ, and these data should not be used for human risk assessment.” (Stubbs comments, p. 1)

“A joint meeting of the FAO/WHO considered the forestomach tumors induced by chlorothalonil ‘to be a rodent-specific lesion that is not relevant for humans, because of differences in anatomy and function’ (FAO/WHO, 2009). Similarly, DPR concluded that ‘this endpoint is considered not relevant for human risk assessment (DPR, 2008, P. 102).’” (Stubbs comments, p. 3)

**Response 1:**
OEHHA disagrees with the statement that forestomach tumors are not considered relevant for human risk assessment. The International Agency for Research on Cancer (IARC) addresses the relevance of rodent forestomach tumors to human cancer risk in the technical publication entitled “Predictive Value of Rodent Forestomach and Gastric Neuroendocrine Tumours in Evaluating Carcinogenic Risks to Humans” (IARC, 2003).³

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“While humans do not have a forestomach, they do have comparable squamous epithelial tissues in the oral cavity and the upper two-thirds of the oesophagus. Thus, in principle, carcinogens targeting the forestomach squamous epithelium in rodents are relevant for humans. Also, the target tissues for carcinogens may differ between experimental animals and humans and a forestomach carcinogen in rodents may target a different tissue in humans. Furthermore, tumorigenic effects in the forestomach are usually accompanied by similar effects in other tissues, indicating that there may be either general (e.g., genotoxic or receptor interactive) or multiple modes of action.” (IARC, 2003, page 15)

IARC’s observation that tumorigenic effects in the forestomach are usually accompanied by similar effects in other tissues also holds for chlorothalonil. As discussed in the technical support document forming the basis for the NSRL, in addition to inducing forestomach tumors in rats, chlorothalonil also induces kidney tumors. Also the technical support document provides data indicating that multiple mechanisms are likely to be involved in chlorothalonil’s carcinogenicity, including genotoxicity, cytotoxicity, cell proliferation and histone protein binding. Given the multiple mechanisms of action likely to be involved in chlorothalonil’s carcinogenicity, the multiple target tumor sites observed in rats, and the recognition that carcinogens may induce tumors at different sites in experimental animals and humans, OEHHA considers the induction of rodent forestomach tumors in the rat by chlorothalonil to be relevant to human cancer risk.

The most recent Risk Characterization document published by the California Department of Pesticide Regulation (CDPR) was published in 2005. It is available on the Department’s website. It does not contain a statement that forestomach tumors are not relevant to humans but does state that there are “uncertainties associated with the use of forestomach tumors as endpoint for human risk assessment.” Notwithstanding the statement in 2009 by the FAO/WHO (Food and Agriculture Organization/World Health Organization) with regard to forestomach tumors as a rodent-specific lesion not relevant for humans, IARC, the pre-eminent authority in the area of carcinogenicity assessment within the World Health Organization, as noted above, has concluded that squamous forestomach rodent tumors can be relevant for humans. Indeed, IARC has recently published carcinogenicity evaluations of several chemicals that produce forestomach

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tumors in animals and has treated tumors at that site as being relevant to humans (ethyl carbamate, \textsuperscript{5} 1,3-butadiene, \textsuperscript{6} ethylene oxide, \textsuperscript{7} aristolochic acid\textsuperscript{8}).

**Comment 2:** “The data are consistent with a temporal sequence of events starting with irritancy and cytotoxicity, followed by increased cell proliferation, multi-focal ulceration and erosion of the forestomach mucosa, regenerative hyperplasia and hyperkeratosis, ultimately progressing to the formation of gastric tumors within the forestomach.” (Stubbs comments, p. 2)

**Response 2:** As discussed in the technical support document multiple mechanisms are likely to be involved in chlorothalonil’s carcinogenicity, including genotoxicity, cytotoxicity, cell proliferation and histone protein binding. While irritation and cytotoxicity may play a role in forestomach carcinogenicity, other mechanisms cannot be ruled out. With respect to the overall cancer potency of the compound, the majority of the activity associated with the cancer potency underlying the NSRL is based on the kidney tumor response.

**Comment 3:**
“The mechanism of renal tumor induction in rodents has been shown to be a threshold driven process, and clearly demonstrates a non-linear incidence of tumors.” (Stubbs comments, p. 1) The data on cytotoxicity, elevated cell proliferation, and tubular cell hyperplasia “strongly support the view that the renal tumors arise via a secondary, non-genotoxic mode of action, which occurs as a direct consequence of prolonged stimulation of cell proliferation following sustained damage to the proximal tubules of the kidney… Repeated administration of chlorothalonil at doses below the threshold for the induction of renal tubular hyperplasia, does not lead to subsequent tumor formation.” (Stubbs comments, p. 6)

**Response 3:**


OEHHA disagrees with the general statement that the induction of renal tumors in rodents has been demonstrated to be a threshold driven process, and also disagrees with the statement as it applies to chlorothalonil. As is true for tumors at other sites, a variety of different mechanisms may be involved in the induction of renal tumors, including genotoxicity, cytotoxicity, and cell proliferation. The technical support document discusses the various mechanisms that may be involved in chlorothalonil carcinogenesis, based on the available mechanistic data. These include one or more mechanisms involving genotoxicity, one or more involving cell proliferation, and another involving histone protein binding. The statement that there is clear demonstration of non-linear tumor incidence is discussed in response to comment 5.

There are multiple examples of quantitative cancer risk assessments on chemicals that induce rodent renal tumors, in which the dose-response at low doses is assumed to be linear. For example, the U.S. Environmental Protection Agency (U.S. EPA) has applied the linearized multistage model (a non-threshold model) to renal tumor data to estimate cancer dose-response relationships and risk for various chemicals, including nitrobenzene, bromodichloromethane, and trichloroethylene. In the case of trichloroethylene, which induces kidney tumors in humans and in rodents, the U.S. EPA applied non-threshold models to both the human and the animal kidney tumor incidence data.

**Comment 4:**
“The values for renal tubular adenomas and carcinomas for female rats from Wilson, et al. (1985) presented in Table 2 [of the OEHHA technical support document], are in error. A review of the report (Wilson, et al., 1985) reveals that the overall incidence in females given 0, 40, 80, and 175 mg/kg-day were 0/60, 3/60, 6/59 and 23/60, respectively.” (Stubbs comments, p. 3)

**Response 4:**
The commenter correctly cites the renal tumor incidence data in female F322/N rats reported in the original histopathologic evaluation of renal tissue from the 1985 study by Wilson *et al.* However, a reevaluation of the renal tissue slides was subsequently

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The incidence data from the reevaluation of the renal tissue slides were used in the 2005 CDPR assessment of chlorothalonil. The renal tumor incidence data from the reevaluation are presented in Table 2 of the NSRL technical support document and cited as: “Wilson, 1986, as reported in CDPR, 2005.” Thus, the female F322/N rat renal tumor incidence data presented in Table 2 of the technical support document are correct.

Comment 5:
“The incidences of renal tumors presented graphically in Figure 1 clearly indicate a threshold for tumor formation.” (Stubbs comments, p. 4) Figure 1 is a plot of the dose response data for kidney tumors with the logarithm (log) of dose on the x axis and tumor incidence on the y axis, and without error bars showing uncertainty in the incidence.

Response 5:
The plot on the following page shows dose plotted against tumor incidence (rather than log[dose] plotted against tumor incidence) for the same data as that shown in Figure 1 of the comments. It also includes on the plot the error bars, as a measure of uncertainty in the incidence values. The relationship between dose and incidence shown is the same as that provided in Figure 1 of the comments, but it looks different because a scale linear in dose is used. The figure below illustrates that the data are consistent with linearity in the low dose region.

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OEHHA Figure 1: Tumor Incidence versus Dose for Renal Tumors in F344/N Rats Treated with Chlorothalonil

Linearity in the low dose region can be further assessed by fitting the linearized multistage model to the renal tumor data, and evaluating the fit with the chi-squared goodness of fit test. This is done for the renal tumor incidence data from the Wilson and Killeen (1989)\textsuperscript{15} study in male F344/N rats that were used by OEHHA in deriving the cancer potency estimate for chlorothalonil. This study is referred to in the comments as

the “Wilson et al. (1989)” male rat study, and in Figure 1 of the comment as the “1989 study, male rats.”

When the (linearized) multistage cancer model within the U.S. EPA’s Benchmark Dose Software (BMDS) is fit to the renal tumor incidence data from this study, the p-value for the chi-squared goodness of fit test is 0.9462, indicating an acceptable fit. More specifically, this p value is well above 0.1, which is the cutoff below which the null hypothesis of adequate fit is rejected. Further, this fit corresponds to a model that is entirely linear in dose, since when higher order terms are allowed in the model (such as those corresponding to $d^2$, $d^3$, etc.), the parameters associated with those terms are estimated to be zero, indicating that a simple model linear in dose is sufficient to fit these data. The plot below shows the fitted curve of the model.

**OEHHA Figure 2: Multistage Cancer Model for Renal Tumor Incidence in Male F344/N Rats Treated with Chlorothalonil (Wilson and Killeen, 1989)**
Additionally, when the multistage cancer model within the U.S. EPA’s BMDS is fit to the three other renal tumor incidence data sets shown in Figure 1, the goodness of fit p-values are all well above the 0.1 cutoff (in fact, all were above 0.5), even for the simple model linear in dose. This indicates that a linear approach is adequate for modeling the renal tumor incidence data from each of these four studies.

**Comment 6:**
All of the mechanistic studies “support the conclusion that the carcinogenic response with chlorothalonil [in the kidney] is a threshold phenomenon and the use of a threshold dose model.” (Stubbs comments, p. 5)

**Response 6:**
OEHHA disagrees with the above statement. The technical support document that describes the basis for the NSRL includes a brief review of the genotoxicity data and other data relevant to possible mechanisms of chlorothalonil carcinogenicity. It shows that multiple mechanisms are likely to be involved, including one or more involving genotoxicity, one or more involving cell proliferation, and another involving histone protein binding (See pages 6-9 of the technical support document). As concluded in the technical support document (p. 9), taken together, the mechanistic data for chlorothalonil do not support the rejection of a linear low-dose (i.e., non-threshold) assumption for dose response analysis. Moreover, as discussed in the response to comment 5 above, analysis of renal tumor incidence data from studies in rats indicates the dose-response is consistent with linearity in the low dose region.

The comment presents data from acute renal tubular epithelial cellular toxicity studies in rats (p. 5) to support a cytotoxicity-based cell proliferative mechanism of action for chlorothalonil carcinogenicity, and the use of a threshold dose model. These studies were conducted using dose levels that are greater than (1000 mg/kg-day) or essentially equivalent to (175 mg/kg-day) the highest dose used in the chronic carcinogenesis bioassays that form the basis of the NSRL effects. These high-dose acute toxicity studies do not provide evidence of a threshold, since only a single dose level was tested, and tumors occur at lower doses. These high-dose acute toxicity studies did not assess measures of cell proliferation in the renal tubular epithelium, thus they do not provide evidence for the occurrence of cell proliferation subsequent to cytotoxicity.

As discussed in the NSRL technical support document, chlorothalonil may induce cell proliferation by multiple mechanisms. Cytotoxicity, accompanied by regenerative hyperplasia (a type of cell proliferation) is only one possible mechanism. Another mechanism that is independent of cytotoxicity by which chlorothalonil may induce cell
proliferation involves chlorothalonil’s ability to activate the erythroblastic leukemia viral (ErbB-2) oncogene tyrosine kinase signal transduction pathway, as shown in studies in a human cancer cell line.\textsuperscript{16} Also as discussed in the NSRL technical support document and in the responses to comments 8 and 9 below, chlorothalonil may induce tumors via one or more genotoxic mechanisms. For example, electrophilic thiol metabolites, such as those derived from chlorothalonil-glutathione conjugates, have the potential to react directly with DNA and induce mutations. In addition, chlorothalonil induces oxidative damage to DNA, as indicated by increases in levels of 8-hydroxy-2'-deoxyguanosine (8-OH-2dG), a mutagenic DNA adduct.

**Comment 7:**
In specialized 28-day and 90-day sub-chronic studies in the rat chlorothalonil was shown to increase cell proliferation in the proximal tubule. “There were no effects observed in animals dosed with 1.5 mg/kg/day, demonstrating a clear threshold for repeat-dose effects in the kidney.” (Stubbs comments, p. 6)

**Response 7:**
These studies are not of sufficient length to rule out the possibility of low dose treatment-induced cell proliferation following longer-term chlorothalonil exposure.

**Comment 8:**
With regard to genotoxicity, “…OEHHA relies on sporadic positive results in isolated in vitro assays and other non-standard in vitro tests. Syngenta believes this interpretation ignores the overall weight of evidence that chlorothalonil is not genotoxic, a conclusion that has been reached by other regulatory agencies.” (Stubbs comments, p. 7)

**Response 8:**
OEHHA disagrees with the above statement. Table 1 on page 12 lists the findings of the numerous genotoxicity studies discussed in the NSRL technical support document. These consist of studies identified by OEHHA in a search of the peer-reviewed scientific literature, as well as other studies discussed in the 1999 IARC review of chlorothalonil and the 2005 CDPR risk characterization document on chlorothalonil.

As shown in Table 1, positive findings of genotoxicity of chlorothalonil are neither sporadic, nor limited to \textit{in vitro} tests. Several of the positive tests were included in the CDPR review, and were conducted using standard genotoxicity test guidelines (e.g., \textit{in vitro} gene mutation assays in \textit{S. typhimurium}, \textit{Aspergillus nidulans}, and L5178Y t/k+/–).

\textsuperscript{16} Tessier D, Matsumura F. 2001. Increased ErbB-2 tyrosine kinase activity, MAPK phosphorylation, and cell proliferation in the prostate cancer cell line LNCaP following treatment by select pesticides. \textit{Toxicol Sci} 60:38-43.
mouse lymphoma cells; the \textit{in vitro} chromosome aberration tests in Chinese hamster ovary cells; and the \textit{in vivo} chromosome aberration test in male Chinese hamsters). Other positive findings were observed in genotoxicity assays that, while not part of the set of studies typically required for pesticide registration, are equally valid. For example, the comet assay is recognized as a well-developed and sensitive method to detect DNA damage and strand breaks, and is widely used by many toxicology laboratories internationally.
### Table 1. Chlorothalonil Genotoxicity Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Study Type</th>
<th>Species/strain/cell type</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Vitro</td>
<td>Gene Mutation Assays</td>
<td>S. typhimurium TA102</td>
<td>Positive (+ activation)</td>
<td>IARC 1999; CDPR 2005</td>
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<td></td>
<td></td>
<td>S. typhimurium TA98, TA100,TA1535,TA1537, TA1538</td>
<td>Negative (+/- activation)</td>
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<td></td>
<td></td>
<td>Aspergillus nidulans</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. coli WP2 hcr</td>
<td>Negative (+/- activation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L5178Y t/k− mouse lymphoma cells</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sister chromatid exchange</td>
<td>Chinese hamster ovary (CHO) cells</td>
<td>Positive</td>
<td>IARC 1999; CDPR 2005</td>
</tr>
<tr>
<td></td>
<td>Chromosome Aberration Test</td>
<td>CHO cells</td>
<td>Positive</td>
<td>CDPR 2005; Vigueux et al. 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hamster lung V79 cells</td>
<td>Negative</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mouse BALB/c 3T3 cells</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micronucleus Test</td>
<td>Hamster lung V79 cells</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>Mouse BALB/c 3T3 cells</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comet Assay (DNA damage)</td>
<td>Human lymphocytes</td>
<td>Positive</td>
<td>Lebaillly et al. 1997</td>
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<td></td>
<td>CHO cells</td>
<td>Positive</td>
<td>Vigueux et al. 1998; Godard et al. 1999</td>
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<td>DNA binding</td>
<td>Mammalian DNA</td>
<td>Positive</td>
<td>CDPR 2005</td>
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<td>Mammalian DNA</td>
<td>Negative</td>
<td>CDPR 2005</td>
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<tr>
<td>In Vivo</td>
<td>Chromosome Aberration Test</td>
<td>Male Chinese hamsters, bone marrow</td>
<td>Positive</td>
<td>CDPR 2005</td>
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<td>Male Chinese hamsters, bone marrow</td>
<td>Negative</td>
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<td>Rats, bone marrow</td>
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<td>Mice, bone marrow</td>
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<tr>
<td></td>
<td>Micronucleus Test</td>
<td>Male Chinese hamsters, bone marrow</td>
<td>Negative</td>
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<td>Rats, bone marrow</td>
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<td></td>
<td></td>
<td>Mice, bone marrow</td>
<td>Negative</td>
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<tr>
<td></td>
<td>Comet Assay (DNA damage)</td>
<td>Human male farmers, mononuclear leukocytes</td>
<td>Positive</td>
<td>Lebaillly et al. 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male Sprague-Dawley rats</td>
<td>Negative</td>
<td>Godard et al. 1999</td>
</tr>
</tbody>
</table>
Comment 9:
“[T]he presence of slightly higher levels of 8-OH-2-dG (approximately 2.5-fold above background) may reflect a depletion of the GSH levels in liver leading to a reduced capacity to scavenge spontaneous ROS [reactive oxygen species]…ROS ‘are expected to have a range of low doses that have no biologically significant consequences.’ In light of this, it should be noted that the mechanism of action of chlorothalonil is consistent with a threshold phenomenon.” (Stubbs comments, pp. 8)

Response 9:
The comment refers to the study of Lodovici et al. (1997), in which levels of the oxidized DNA adduct, 8-OH-2dG, were measured in the livers of rats treated for 10 days with chlorothalonil at doses of 0, 0.1, 0.13, 0.5, or 1.0 milligrams per kilogram per day (mg/kg/d). The 2.5-fold increase in liver 8-OH-2dG above background referred to in the comment is the increase observed in the group of rats treated with the lowest chlorothalonil dose (i.e., 0.1 mg/kg/d). In fact, a dose-dependent increase in liver 8-OH-2dG levels was observed in this study, with a 3-fold increase in the 0.13 mg/kg/day treatment group, a 3.8-fold increase in the 0.5 mg/kg/day treatment group, and a 4.5-fold increase above background in the 1.0 mg/kg/day treatment group. It is inaccurate to characterize these dose-dependent increases in liver 8-OH-2dG induced by in vivo exposure to relatively low levels of chlorothalonil as “slightly” above background. In addition, the data reported by Lodovici et al. (1997) provide no evidence for the existence of a dose threshold below which no increase in liver 8-OH-2dG levels would occur. Moreover, as discussed in the NSRL technical support document, 8-OH-2dG adducts are just one manifestation of oxidative DNA damage. If not repaired, these adducts may lead to the formation of single point mutations and DNA strand breaks.

Comment 10:
“OEHHA cites a report by Baccarelli and Bollati (2009) to speculate on possible alternative mechanisms that could result from the binding of chlorothalonil to histones. We believe that human risk assessment decisions based on unsubstantiated speculation is inappropriate.” (Stubbs comments, p. 9)

Response 10:
As discussed in the responses to comments 2 and 5, chlorothalonil may induce tumors through a variety of different mechanisms. The NSRL technical support document discusses several possible mechanisms, including one or more involving genotoxicity, one or more involving cell proliferation, and another involving histone protein binding. In discussing the evidence for histone protein binding and the implications with regard to
carcinogenicity, OEHHA referenced the review article by Baccarelli and Bollati (2009), which describes the vital functions carried out by histones in DNA replication, transcription, folding, and packaging. OEHHA’s approach to the cancer dose response assessment of chlorothalonil was not based on the observation that chlorothalonil binds to histones, however. Rather, the decision was based on a review of the genotoxicity data and other data relevant to possible mechanisms of chlorothalonil carcinogenicity, and the conclusion that multiple mechanisms, including one or more involving genotoxicity are likely to be operative. Thus data are not adequate to depart from the low dose linearity default.

Comment 11:
Debbie Stubbs proposed that “OEHHA reconsider the proposed NSRL using a threshold model for determining the NSRL.” (Stubbs comments, p. 10)

Response 11:
For the reasons stated above in responses to comments 3, 5, 6, 8, 9, and 10, OEHHA finds that there is no basis for using a threshold model for determining the NSRL for chlorothalonil.

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.5(a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected persons, than the proposed regulation. OEHHA has determined that the alternative approach to calculating the NSRL proposed in the public comments has an insufficient scientific basis and would not comply with the guidance provided in the regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses “no significant risk” of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to provide a “safe harbor” level for a particular chemical exposure. This regulation establishes the numerical No Significant Risk Level for one
carcinogen, chlorothalonil. At or below this level, the Act does not require a warning regarding cancer or prohibit discharges to sources of drinking water based on carcinogenicity concerns associated with chlorothalonil. Thus, this level will allow persons subject to the Act to determine whether a given discharge to sources of drinking water or exposure to people involving these chemicals is subject to the warning requirement and discharge prohibition provisions of the Act related to the risk of cancer (Health and Safety Code sections 25249.6).

Although section 25703 describes principles and assumptions for conducting risk assessments to derive safe harbor levels, many businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees needs the ability to determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Given the use of the chemical covered by this regulation, the absence of this regulation would leave numerous businesses without an efficient way of determining if they are in compliance with the Act without the expenditure of significant resources on their part.

**LOCAL MANDATE DETERMINATION**

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. It should be noted that Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.