Department of Pesticide Regulation

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MEMORANDUM

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SUBJECT: DEVELOPING MITIGATION MARGINS OF EXPOSURE FOR NON-FUMIGANT PESTICIDES WITH THRESHOLD EFFECTS

I. Introduction

The California Department of Pesticide Regulation (DPR) conducts human health risk assessments on pesticides to determine if health risks are associated with their legal uses (CDPR, 2017). To that end, the Human Health Assessment (HHA) Branch analyzes information on the health hazards of a pesticide (i.e., toxicity), evaluates individual activities associated with the pesticide's uses (i.e., exposure), and summarizes findings on the projected health concerns in a Risk Characterization Document (RCD). Based on the findings presented in the RCD and the priorities set forth in a Risk Management Directive (RMD), the Human Health Mitigation Program in the Worker Health and Safety (WHS) Branch develops measures to reduce the health risks identified in a set of exposed individuals to levels that are below the level of concern. Pesticides can be categorized as fumigant or non-fumigant based on their uses, and may induce health effects with or without a threshold (i.e., existence of a safe dose). Because of the unique physiochemical properties of fumigants (e.g., high vapor pressure, i.e., $\geq 10^{-4}$ mmHg), and the challenge of establishing definitive safe levels for non-threshold effects (e.g., carcinogenicity), risk reduction of the specific exposure and health concerns for fumigants requires a different approach than for non-fumigants. Hence, only non-fumigant (i.e., conventional) pesticides with threshold health effects will be addressed in this document.

II. Characterizing Risk of Conventional Pesticides with Threshold Effects

In order to characterize the health risks associated with exposure to conventional pesticides with threshold effects, the approach of margin-of-exposure (MOE) is used (NRC, 1994). The MOE is the point-of-departure (PoD) divided by the anticipated level of exposure. The PoD is either a no-observable-effect-level (NOEL) selected from an appropriate toxicological study, or a benchmark dose (BMD) computed using scientifically sound mathematical models as detailed in the RCD (USEPA, 2012a; USEPA, 2016a; USEPA, 2016b). The anticipated exposure level is specific to the types of exposed individuals (i.e., handlers, reentry workers/residents, or bystanders), the durations of exposure (i.e., short-term, intermediate-term, or long-term), and the routes of exposure (i.e., dermal, inhalation, and (or) ingestion) (Beauvais *et al.*, 2007; USEPA, 2012b; USEPA, 2013; Kwok, 2017), and is developed based on the pesticide's legal uses as prescribed on the product labels. Thus, the formula used to calculate MOEs is as follows:

$$\text{MOE} = \frac{\text{PoD (i.e., NOEL or BMD)}}{\text{Exposure}}$$

Where:
MOE: margin-of-exposure (dimensionless)
PoD: point-of-departure derived from NOEL or BMD (mg/kg/day)
Exposure: anticipated level of exposure (mg/kg/day)

III. Mitigating Pesticide Exposure Risks

During mitigation development, WHS staff use the MOEs found in the RCD (i.e., "RCD" MOE) or request updated MOEs from HHA (McCarthy and DuTeaux, 2018) for identifying the health risks of concern. However, if additional MOE calculations are needed (e.g., a new exposure scenario emerges after RCD completion), "identical" exposure algorithms, computer models, databases, and defaults should be employed in order to maintain an internal consistency between the exposure estimates generated by the RCD process and the mitigation process. Significant deviations from the RCD methodology during mitigation would introduce variation in the exposure estimates, rendering the resulting MOEs difficult to interpret. Once all relevant "RCD" MOEs are compiled, WHS staff will use the following "mitigation" formula as guidance for achieving a target MOE:

$$\text{Target MOE} = \frac{\text{PoD (i.e., NOEL or BMD)}}{\text{Exposure} \times (AF_1 \times AF_2 \times \ldots \times AF_i)}$$

Where:

Target MOE:	MOE value as specified in the RMD
PoD:	point-of-departure derived from NOEL or BMD ("constant")
Exposure:	anticipated level of exposure
AF_1:	adjustment factor 1 for exposure reduction
AF_2:	adjustment factor 2 for exposure reduction
AF_i:	adjustment factor i for exposure reduction

The target MOE is specified in the RMD to address the health risks associated with the exposed individual identified in the RCD. In general, the target MOE is set at 100 for PoD values derived from experimental animal studies, or 10 for PoD values derived from controlled human studies (note: variations to these defaults can occur due to regulatory mandates, such as the State of California Toxic Air Contaminant Identification and Control Act [AB 1807, Tanner 1983] or the Federal Food Quality Protection Act). Hence, exposure scenarios with MOE values below the target (i.e., exceeding the level of health concern) will be subject to risk reduction. Based on the MOE computation formula above, the health risk reduction, in principle, can be achieved by modifying the PoD and (or) anticipated exposure. However, PoD modifications are beyond the scope of developing risk reduction measures because the NOEL or BMD value used in the MOE calculation was peer-reviewed by external stakeholders (e.g., Office of Environmental Health Hazard Assessment and U.S. Environmental Protection Agency [U.S. EPA]) and approved by DPR management during the risk assessment process. Accordingly, modification to the exposure component is the "only" option available to achieve risk reduction. This process is described below.

Since the anticipated exposure level is specific to different exposed individuals, durations, and routes, information entered into the "Exposure" term in the formula above may vary. In fact, the "Exposure" term is a multiplication product of a set of factors. For example, when calculating agricultural handler exposure to a pesticide (Beauvais *et al.*, 2007), the "Exposure" term includes two multiplicative exposure factors: (1) the pesticide application rates and (2) the number of acres treated per day. By comparing the "RCD" MOE to the target MOE, these two exposure factors could be modified individually or collectively to achieve the overall exposure adjustment needed. That is, if the "RCD" MOE is 10-fold below the target MOE (e.g., 100), an overall 10-fold upward adjustment is needed for the "RCD" MOE. This adjustment can be achieved through a 10-fold reduction to either one of the two exposure factors, a 2-fold reduction to the first exposure factor combined with another 5-fold reduction to the second exposure factor, or a 3.3-fold reduction to both exposure factors, and so on. Hence, in the "mitigation" formula above, a series of adjustment factors is included to reflect the fact that exposure reduction can be achieved via adjustment of a particular factor or a set of factors. However, the actual allocation of adjustment factor(s) will be based on technological feasibility (e.g., product efficacy), socioeconomic factors, and additional information obtained from stakeholders (e.g., other regulatory agencies, environmental groups, and regulated communities).

It is noteworthy that not all factors entered into the exposure calculation are amenable to adjustment such as physiological factors, e.g., body weight and absorption fraction.

$$\text{Exposure} = \frac{\text{Unit Exposure Rate}\left(\frac{\mu g}{\text{lb A.I.}}\right) \times \frac{\text{Acre Treated}}{\text{day}} \times \text{Application Rate}\left(\frac{\text{lb A.I.}}{\text{acre}}\right)}{\frac{\text{Body Weight (kg)}}{\text{Absorption Fraction}}}$$

Physiological factors are regulatory defaults based on DPR exposure assessment policies (Donahue, 1996; Andrews and Patterson, 2000; Cochran, 2008), and should only be modified after consulting with DPR upper management. The factors that are amenable to adjustment for reducing exposure for the different categories of exposed individuals (i.e., handlers, re-entry workers, and bystanders) are identified and described below. Based on these adjustable factors, options available for exposure reduction are summarized in Figure 1 on page 9.

A. Handlers (Mixer/Loaders/Applicators) - Occupational and Non-Occupational

In the RCD, exposure estimates (expressed as doses [mg/kg/day]) are presented for each of the exposed individuals under different exposure durations: short-term (i.e., short-term absorbed daily dose [STADD]), intermediate-term (i.e., Seasonal Average Daily Dose [SADD]), and long-term (Annual Average Daily Dosage [AADD]) (definitions of these exposure durations and dose values have been detailed in Kwok (2017)). Hence, the mitigation measure development is based on this format. Also, factors that are not amenable to adjustment will be labeled as "constant."

For handlers (i.e., mixers/loaders/applicators), STADD (mg/kg/day) can be calculated as follows (Beauvais *et al.*, 2007; USEPA, 2012b):

$$\text{STADD} = \frac{\sum(\text{UnitER} \times \text{AF}) \times \text{AT} \times \text{AppRate}}{\text{BW}}$$

Where:

UnitER:	short-term dermal or inhalation unit exposure rates (μg/ lb A.I.)
AT:	maximum area treated per day (area unit [e.g., acres or square feet]/day)
AppRate:	maximum pesticide product application rate (lb A.I./area)
AF:	dermal or inhalation absorption factor (dimensionless; "constant") (Donahue, 1996; Cochran, 2008)
BW:	age-specific body weight (kg; "constant") (Andrews and Patterson, 2000)

Based on this equation, exposure reduction can be achieved by modifying (1) the unit exposure rates, (2) the area treated per day, and (or) (3) the amount of pesticide applied per unit area (note: AF and BW are physiological factors and should be treated as "constant" for the purpose of mitigation development). The unit exposure rates are application method- and product formulation-dependent. Hence, exposure reduction can occur by using "smaller" unit exposure rates (i.e., changing to another application method or formulation) or by using the same application method and (or) formulation with additional personal protection equipment (PPE) beyond that specified on the product label. However, since pesticide products designed for use in non-occupational (i.e., residential) settings usually have no PPE requirements, exposure reduction through PPE may not be applicable for residential handlers.

To assess the pesticide exposure for a longer term (i.e., intermediate term or SADD), the same exposure formula applies, except that a long-term exposure unit rate and central estimate (i.e., mean) are used in lieu of a short-term exposure unit rate and maximum value (for AT and AppRate). To assess a long-term exposure (i.e., AADD), the SADD is adjusted based on the annual use per 12 months. Hence, the only factor amenable to adjustment for reducing long-term exposure is the annual use per year (i.e., number of months of use per year).

B. Post-Application Reentry – Occupational, Non-Occupational, and Residential

Akin to handlers, the STADD (mg/kg/day) due to reentry exposure can be expressed as (USEPA, 2013; Beauvais, 2014):

$$\text{STADD} = \frac{\text{RES} \times \text{TC} \times \text{AF} \times \text{ET}}{\text{BW}}$$

Where:

RES:	surface transferable residue from crops (i.e., dislodgeable foliar residue [DFR]), turf grasses (i.e., transferable turf residue [TTR]), or indoor surfaces (i.e., indoor surface transferable residue [TR]) (μg/cm^2)
ET:	activity-specific exposure time (hours)
TC:	transfer coefficient (cm^2/hr; "constant") (USEPA, 2013; Kwok, 2016)
AF:	inhalation or dermal absorption factor (dimensionless; "constant") (Donahue, 1996; Cochran, 2008)
BW:	age-specific body weight (kg; "constant") (Andrews and Patterson, 2000)

Based on this equation, exposure reduction can occur by modifying (1) the residue and (or) (2) the exposure time (note: TC values are regulatory defaults and should be treated as "constant" for the purpose of mitigation development). Also, the amount of pesticide remaining on the treated surface is a function of the time interval between the initial application and reentry. Hence, depending on the exposed individuals of concern, exposure time modification translates into shorter work hours (e.g., occupational reentry workers) or longer "waiting" time prior to reentry (e.g., residential bystanders). Akin to the exposure time, modification to the pesticide application rate translates into reductions of DFR for agricultural reentry workers, TTR for residential bystanders, and TR for residents. To protect agricultural workers, some pesticide labels specify a reentry interval (REI), during which entry into the treated field is prohibited. Since DFR reduction is also a function of time (Andrews, 2000), exposure reduction for agricultural reentry workers can occur by modifying the REI (i.e., DFR is reduced when there is a longer time interval for pesticide residue to dissipate from treated foliage). However, for non-agricultural occupational reentry or residential post-application, neither reentry interval restrictions nor protective clothing are required. Hence, using protective clothing requirements to reduce exposure for reentry activities should only be performed after consulting with DPR upper management.

To assess the pesticide exposure for a longer term (i.e., intermediate-term or SADD), the same exposure formula applies, except that a central estimate (i.e., mean) is used in lieu of a maximum value for the residue (Beauvais, 2008). For assessing a long-term exposure (i.e., AADD), the SADD is adjusted based on the annual use per year per 12 months. Hence, the only factor amenable to adjustment for reducing long-term exposure is the annual use per year (i.e., number of months of use per year).

C. Bystanders – Occupational and Residential

Bystander exposure to conventional pesticides can be due to off-site movement via spray drift, soil-to-air transfer after application (i.e., re-volatilization), and (or) contact with treated surfaces. Because different sets of exposure factors are involved, two formulas of STADD (mg/kg/day) are needed for characterizing the inhalation and non-inhalation exposures.

1. Inhalation Route:

$$\text{STADD} = \frac{\text{TWA} \times \text{BR}}{\text{BW}}$$

Where:

TWA:	time weighted average air concentration (μg/m^3)
BR:	breathing rate (m^3/day "constant") (Andrews and Patterson, 2000)
BW:	age-specific body weight (kg; "constant") (Andrews and Patterson, 2000)

2. Non-Inhalation Routes (i.e., dermal and incidental ingestion):

$$\text{STADD} = \text{RES} \times \text{F} \times \text{EAG}$$

Where:

RES:	residue (μg/cm^2)
F:	deposition fraction (dimensionless)
EAG:	exposure algorithm ("constant") (USEPA, 2012b)

Based on these two equations, exposure reduction can occur by modifying (1) the air concentration, (2) the residue, and (or) (3) the deposition fraction (BR and BW are physiological factors and EAG is a set of standardized model algorithms for characterizing age- and activity-specific exposures. Both should be treated as "constant" for the purpose of mitigation development). However, unlike the handler and post-application reentry scenarios, the air concentration and deposition fraction entered into mitigation development can only be generated by computer models: AGricultural DISPersal near-wake Lagrangian model (AGDISP) (Teske and Curbishley, 2013) for aerial applications (e.g., fixed-wing or rotary-wing aircrafts) and Agricultural spray DRIFT model (AgDRIFT) (Teske et al., 2002) for ground applications (e.g., ground boom and airblast). If needed, further adjustments to the air concentration and fractional deposition from aerial applications can be made by modifying the tank-mix as described in the study by Jiang and Barry (2018). To reduce inhalation exposure to re-volatilized pesticides, and considering the potential contribution to the air concentration from multiple fields, the effectiveness of mitigation measures can only be assessed using air dispersion models (e.g., AERMOD atmospheric dispersion modeling system (Alan *et al.*, 2005)) coupled with population-based exposure assessment models (e.g., High End Exposure Version 5 Crystal Ball [HEE5CB]) (Johnson, 2009). It is noteworthy that exposures for longer terms (i.e., intermediate-term [SADD] and long-term [AADD] are not common in bystanders. Hence, mitigation measures will only be developed on a case-by-case basis.

In terms of workflow, WHS staff will identity all relevant computer-modeling tasks mentioned above and request assistance from the Environmental Monitoring Branch during this phase of mitigation development.

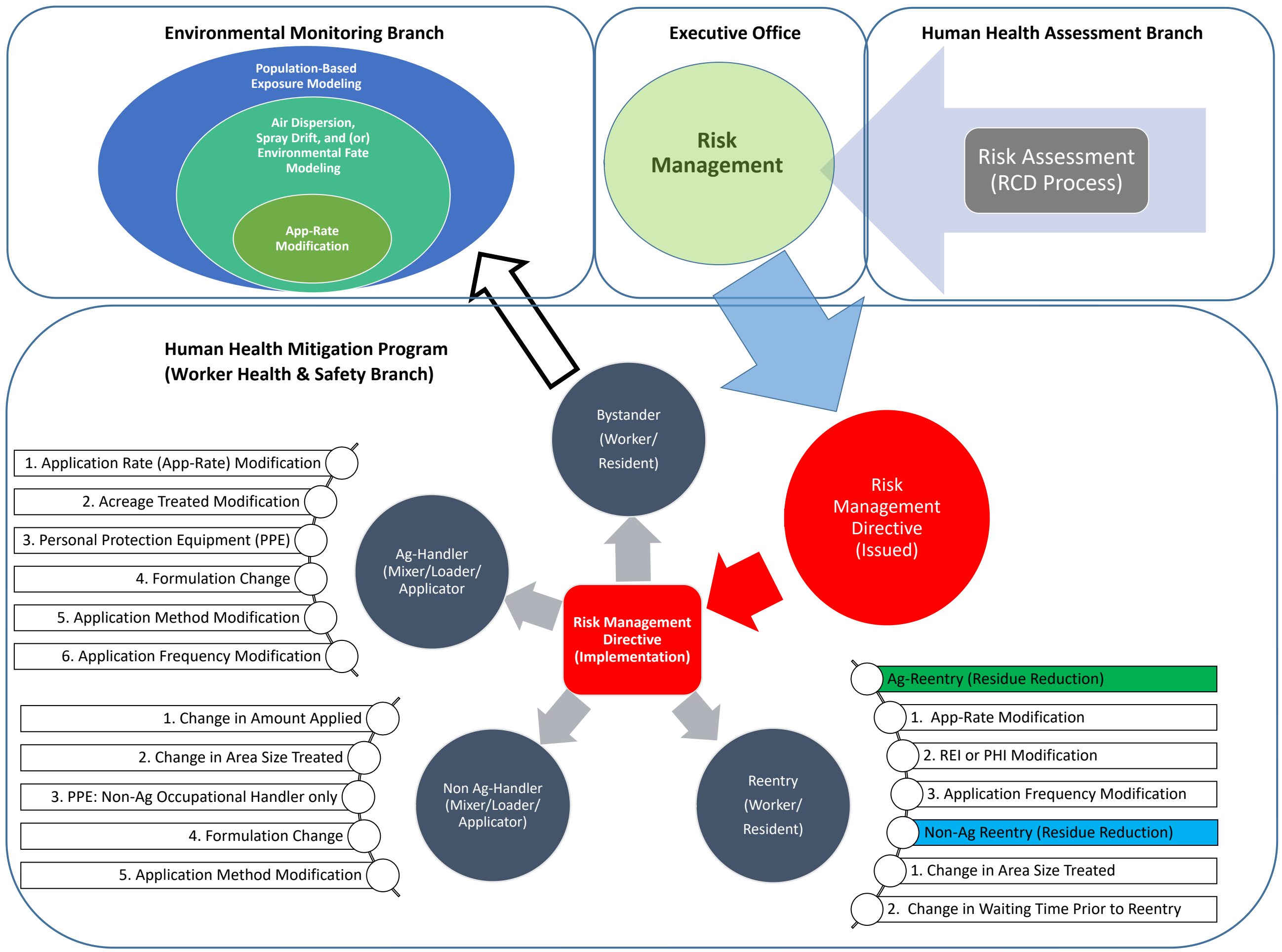

Figure 1: Potential options for exposure reduction in different exposed individuals

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