MEMORANDUM

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SUBJECT: Response to the Fipronil Task Force Request for Reconsideration of Findings in DPR's Draft Human Exposure Assessment for Fipronil

Background

The Fipronil Task Force, LLC (FTF), comprised of 10 fipronil registrants, submitted a Request for Reconsideration of Findings to the Department of Pesticide Regulation (DPR) on May 20, 2021. The FTF submission outlines specific comments that the task force believes merit reconsideration in the finalization of the Exposure Assessment Document (EAD) and the Risk Characterization Document (RCD).

This memorandum provides DPR's responses to the FTF comments on the Dermal Absorption Value and the specific assumptions in the exposure assessment including those for pet product applicators and transferable residue from pet products. Responses specific to the critical acute and subchronic points of departure are detailed in a separate memo covering toxicity and risk characterization.

Note that references cited in this memorandum are specific to the FTF Request for Reconsideration or DPR's response, and not necessarily duplications of those in the draft or final EAD. Likewise, every effort has been made to ensure that any references to tables found in the draft or final EAD are clear. Tables specific to this memorandum are numbered independently of the EAD. Every effort has been made to directly quote the FTF comments, however some have been condensed for brevity.

Request for Reconsideration: Dermal Absorption

FTF Comment: …[B]ased on the weight-of-evidence, the available data support a dermal absorption value of 1% as reported and supported by EPA (2020) in their most recent draft fipronil risk assessment. Additionally, 1% is considered to be a conservative value as it is rounded up from the highest directly absorbed value of 0.65% in the rat, which has skin

generally accepted to be 3-10 times more permeable than human skin (OECD 2019; EFSA 2017).

DPR Response: DPR carefully reviewed all the relevant data including the fipronil dermal absorption study from Cheng (1995), as well as various guidance on dermal absorption studies from US Environmental Protection Agency (US EPA), the Organization for Economic Co-operation and Development (OECD), and the European Food Safety Authority (EFSA) as referenced by FTF (Cheng, 1995; US EPA, 1998; EFSA, 2017; OECD, 2019). DPR concludes that the dermal absorption rate of 4.3% is scientifically supported as explained below.

Based on the study by Cheng (1995), FTF suggested treating the skin-retained fipronil as bound residue, excluding this portion from the absorbed dose. FTF also stated that fipronil dermal absorption was complete at 24 hours. However, these suggestions are not necessarily supported by data from Cheng (1995). First, while the study measured fipronil absorption by quantifying ^{14}C-radioactivity distributed in different compartments (e.g., urine, feces), the investigators did not use techniques such as tape stripping that would quantify the amount of fipronil in *stratum corneum*. Second, all test animals were sacrificed immediately after the dermal exposures (Table R.1.) such that the release of skin-retained fipronil to the rest of the body could not be determined (US EPA, 1998). Without additional data to determine the bioavailability of skin-retained fipronil, it is a conservative but not unreasonable assumption that all skin-retained fipronil is bound in the skin, and therefore available for further systemic absorption over time.

The study results found in Cheng (1995) imply that dermal absorption was not complete 24 hours after exposure. This study tested fipronil dermal absorption at three dosing rates (70, 668 and 3880 µg/cm^2). Directly absorbed fipronil, represented by the total percentage of radioactivity in blood, cage wash, cage wipe, carcass, feces and urine, is summarized in the Table R.1, below. For the 70 and 3880 µg/cm^2 dosing groups, no trend for the direct-absorbed dose over time could be identified, as the results exhibited large variations (discussed below). For the 688 µg/cm^2 dosing group, directly absorbed fipronil, as the percentage of the administered dose, increased from 0.02% at 10-hr to 0.40 % at 24-hr, implying that absorption was not complete.

Table R.1. Directly-absorbed fipronil represented as mean percent ^{14}C-radioactivity recovered after different durations of ^{14}C-fipronil dermal exposure

Duration of exposure (hr)	Mean percent (%) radioactivity from blood, cage wash, cage wipe, carcass, feces and urine[a]		
	Dermal Dose		
	70 µg/cm^2	**668 µg/cm^2**	**3880 µg/cm^2**
0.5	< 0.005 (NA[b])	< 0.005 (NA)	< 0.005 (NA)
1	0.07 (0.14)	0.06 (0.16)	0.64 (0.97)
2	0.46 (0.67)	0.05 (0.11)	0.05 (0.10)

4	< 0.005 (NA)	0.10 (0.13)	0.07 (0.14)
10	0.65 (0.34)	0.02 (0.03)	0.18 (0.26)
24	0.36 (0.06)	0.40 (0.11)	0.07 (0.14)

Data cited from Cheng (1995).
a: results are reported as mean (standard deviation);
b: not applicable.

According to the OECD guidance (2019), "*an in vivo dermal absorption study can be considered to have demonstrated completion of absorption if 75% of the material absorbed by the end of the study (material in excreta + exhaled gasses + the carcass excluding application site) is present in the excreta or systemic compartment before the mid-point of the study.*" The Cheng study did not meet these criteria. If there is no evidence demonstrating complete dermal absorption, current guidance suggests using the skin-retained residue as the absorbed dose (EFSA, 2017; OECD, 2019).

FTF cited average values from Cheng (1995). However, it should be noted that the individual replicates (rats) showed considerable variation in fipronil absorption, even with the same dosing rate and exposure period (see the Table R.1 above and R.2 below). FTF also suggested removing a high dermal absorption percentage value (17.2%), considering it an outlier. However, the study report of Cheng (1995) only noted a single outlier of 5.75% at 1 hour post dose in Group 5 without providing any further explanation. DPR considers the full breadth of individual data points when conducting its assessments. Discounting data variations or removing "outliers" without considering statistical or biological significance is not scientifically justifiable and does not follow current guidance (OECD, 2019; EFSA, 2017).

Table R.2. Absorbed ^{14}C-radioactivity recovered after different periods of ^{14}C-fipronil dermal exposure

Duration of exposure (hr)	Mean percent (%) radioactivity from blood, cage wash, cage wipe, carcass, feces and urine, and left on/in the skin after skin wash[a]		
	Dermal Dose		
	70 µg/cm^2	**668 µg/cm^2**	**3880 µg/cm^2**
0.5	1.14 (0.72)	0.61 (0.37)	0.35 (0.20)
1	1.58 (0.57)	5.82 (7.74)	1.44 (0.87)
2	2.91 (0.95)	0.90 (0.12)	0.40 (0.24)
4	1.86 (1.16)	1.65 (1.36)	0.83 (0.45)
10	2.52 (0.53)	1.59 (0.54)	0.87 (0.34)
24	2.19 (0.10)	3.69 (1.04)	0.55 (0.26)

Data cited from Cheng (1995).
a: results are reported as mean (standard deviation);
b: not applicable.

Based on the above discussions, DPR considers dermal absorption rate of 4.3% from Thongsinthusak (1999) an appropriate value. In general, DPR 1) considered the skin-retained fipronil as part of the absorbed dose, 2) used values from 10-hr exposure, which is the time interval in the experimental model closest most similar to the handler exposure period (8 hr), and 3) extrapolated the dermal absorption rate from the tested dosing rates to lower rates because the tested doses were higher than the estimated fipronil dermal exposures. DPR determined this method is reasonable, and complies with current regulatory guidance, including the ones mentioned by the reviewers. The 1% dermal absorption rate proposed by FTF was not backed by either experiment data or regulatory guidance, and there is no evidence supporting to exclude skin-retained fipronil from absorbed dose.

Request for Reconsideration - Applicator: pet groomer and home user

FTF Comment: The applicator assessments included in the draft RCD presented a review of registrant-submitted studies and the available literature. DPR selected a registrant-submitted study (Meo et al, 1997a) to estimate exposure for the professional pet groomer and home user based on "the data quality and completeness" (DPR, 2021) of the study… This same study was cited by DPR as being used for both the spray and spot-on assessments. However, this study only pertained to spray applications. Nonetheless, based on the description of the spot-on study and results as presented in the draft RCD, the correct study does appear to have been used for the spot-on product application assessment (Meo et al, 1997b). Both studies utilized sixteen groomers and each groomer treated eight dogs (except one groomer using the spray product that treated nine dogs) (Meo et al, 1997a and 1997b). The groomers wore a whole-body long underwear suit as the dosimeter along with work clothing and PPE over the undergarments, as well as a pair of cotton gloves underneath the label-required latex gloves when treating dogs. The cotton dosimeter suit and cotton gloves absorb residues and also have larger surface areas than the skin due to the nature of the weave, both serving as inherent conservatisms in the study design.

DPR Response: Different studies were used to assess applicator (professional pet groomer and home user) exposures from spray and spot-on products. For spray products, DPR used a study from Meo *et al.* (1997b), and for spot-on products, DPR used another study from Meo *et al.* (1997a).

FTF cited a study from de Fonteney (1998) to demonstrate that hands with cotton gloves (e.g., cotton dosimeters) collected more fipronil residues than bare hands. After further review of this study, DPR would like to clarify that de Fonteney (1998) was conducted in a post-application setting where cotton gloves were in direct contact with the treated animals. In contrast, for the groomer and pet owner exposure assessment, cotton gloves were worn

under latex gloves and used as a dosimeter to collect the amount of fipronil that penetrated through the gloves (Meo et al., 1997a; Meo et al., 1997b).

FTF Comment, continued: …[S]hort-term exposure, expressed as short-term absorbed daily dose (STADD), represents the highest exposure an individual may realistically experience while performing a label-permitted activity (Frank, 2009). An upper-bound estimate (e.g., 95th percentile of exposure or environmental concentration) was used in the draft RCD to calculate the daily short-term exposure (i.e., seven days or less) for pet groomers and home users per DPR's standard methodologies (Powell, 2002; Beauvais et al, 2007; Kwok, 2017) … The NAS review of DPR's risk assessment process included comments on this specific guidance from Frank (2009), stating "the actual guidance is for only one aspect of the exposure estimate—the source concentration—and prescribes an approach that often results in a value greater than the 95th percentile (Frank 2009). Several further assumptions used to calculate the exposure of at-risk persons push well beyond the 95th percentile and postulate a series of circumstances that may be individually plausible but collectively are implausible" (NAS, 2015). In fact, DPR noted of its own guidance that "it is recognized that the assumed lognormal distribution may not exactly match the actual distribution of exposure values, and that any discrepancy from the lognormal distribution will be greatest at the upper extremes (Ott, 1990)" (Powell, 2009). Therefore, per the NAS review as well as DPR's own guidance, the lognormal distribution does not match the true exposure distribution… For these reasons, the maximum measured exposure (26347 µg/g) should be used for the assessment of the spray as it was for the spot-on.

DPR Response: DPR used upper-bound exposure estimates to assess short-term exposures (STADDs), which represent "*the highest exposure an individual may realistically experience while performing a label-permitted activity*" (Frank, 2009). As explained in the same memo, either the estimated 95th percentile value or the maximum measured value could be considered the upper-bound exposure value, depending on which one is higher. The method to estimate the 95th percentile value assumes that the data are lognormally distributed. DPR conducted Shapiro-Wilk tests to confirm that the exposure data used are indeed lognormally distributed. This information was added into the footnotes of all relevant tables in the final EAD.

For applicator scenarios for pet spray and spot-on products, all parameters were based on values derived from survey studies and represented realistic fipronil use conditions for applicators (groomers and home users), except the unit exposures for which the upper-bound values (e.g., 95th percentile) were used for short-term exposure estimation. For pet groomers, this assessment assumed each groomer treats 10 dogs per day. This number is based on a registrant submitted survey which showed that each commercial groomer treated an average of 9.6 pets per day during flea season (Irwin, 1997). Professional groomers spent an average of 7 minutes to treat one dog for pet spray and 3 minutes for the spot-on product (Meo *et al.*, 1997a; Meo *et al.*, 1997b). For pet owners, this assessment assumed that there were two dogs per household. This is based on the survey results from American Veterinary Medical Association, which showed an average of 1.6 dogs per dog-owning household (AVMA,

2012; AVMA, 2018). In conclusion, for short-term exposures, DPR used the upper-bound estimates (95th percentile estimates or maximum measurements) considering the finite number of applicators monitored in the selected studies and the log-normal distribution of the measured exposure data. All other parameters used (cat/dog size, surface area, contact time, etc.) were determined based on survey studies or recommendations found in the US EPA SOP (2012).

Request for reconsideration - Post-application: pet product – transferable residue

FTF Comment: The post-application assessments presented in the draft RCD relied on registrant-submitted studies to determine the dislodgeable fipronil residue (de Fontenay et al, 1997a, 1997b, 1997c, and 1997c; Hughes, 1997a, 1997b, 1997c, and 1997c). In order to assess the spray, DPR used 2.2% (95th percentile of the lognormal distribution of the exposure) for the short-term absorbed daily dose (STADD) and 1.37% (mean) for the seasonal average daily dose (SADD). These data came from the highest dislodgeable residue data, which were determined at 4-hours in six beagle dogs (cited as de Fontenay et al, 1997a, however, this reference pertains to spot-on treatment to cats and appears to be an error. In order to assess the spot-on, DPR used 16.77% (95th percentile of the lognormal distribution of the exposure) for the short-term absorbed daily dose (STADD) and 6.46% (mean) for the seasonal average daily dose (SADD). These data came from the highest dislodgeable residue data, which were determined at 1-hour in six cats (cited as de Fontenay et al, 1997c in the draft RCD). However, this reference pertains only to spray treatment of dogs and appears to be a citation error in the draft RCD. It should be noted that for both the spray and spot-on the estimated 95th percentiles of the lognormal distribution of dislodgeable residue that were used in the draft RCD risk assessment was higher than the maximum measured values. Specifically, a 95th percentile of the lognormal distribution of the dislodgeable residue of 2.2% compared to maximum measured of 2.06% for the spray and a 95th percentile of the lognormal distribution of the dislodgeable residue of 16.77% compared to maximum measured of 13.63% for the spray. After treatment, the study investigator wore a cotton glove and petted the whole-body surface of the dog with the glove-wearing hand by stroking five times from the head to the tail (i.e., one stroke each on the back, right and left flank, and right and left side of the ventral zone).

DPR Response: All studies considered to derive the dislodgeable fraction values are summarized in Tables 20 and 27 of the EAD. For each formulation (spray or spot-on), the dislodgeable fraction value was only obtained from studies with the same formulation. DPR also revised the post-application exposure assessment for both pet spray and spot-on products in the final EAD. Additional references were also added to the final EAD. In the revised assessment, DPR used 7-day average dislodgeable fipronil residues on pets to estimate resident (adult and child) intermediate-term post-application exposures (SADDs). All the relevant texts and tables in section “IV. EXPOSURE ASSESSMENT” of the final EAD were revised accordingly.

FTF Comment, continued: As per EPA in the Standard Operating Procedures (SOP) for Residential Pesticide Exposure Assessment (2012b), if chemical specific transferable residue (TR) measurements are not available, then a standard value for the fraction of active ingredient available (FAR) for transfer can be used. The standard value is based on the review of eight pet residue transfer ("petting" or "stroking" studies) with a total of nine data sets, that have been submitted to the Agency… It should be noted that three out of four of the transferable residue values calculated in the draft RCD are higher than the US EPA SOP default value for the percentage of dislodgeable fraction that is to be used for both a spray and a spot-on product (EPA, 2012b). This is not unexpected since DPR's values were taken from only the worst-case studies, while EPA's default value is based on a total of nine data sets and therefore is a more realistic case…

DPR Response: DPR did not use the default values from US EPA (2012), because fipronil-specific dislodgeable residues on pets are available. For spray and spot-on products, DPR estimated the dislodgeable residues based on those studies, which have been summarized in Tables 20 and 27. In addition, DPR used different dislodgeable values to estimate short- and intermediate-term exposures, as different POD values were determined for different exposure periods. Detailed discussions of POD values are shown below. Based on these two reasons, using the same default value from US EPA (2012) is the not the best practice for this purpose.

FTF Comment, continued: As described in EPA's draft risk assessment for the registration review of fipronil, two chemical-specific pet residue transfer study data sets (de Fontenay et al, 1997b and Mallipudi, 2012) were combined and plotted using first order decay modeling and then used in the post-application risk assessment (EPA, 2020). It is reported that "the resulting day of application (Day 0) fraction of application rate available for transfer (FAR) value, 0.014 (1.4%) and daily residue dissipation, 0.193 (19.3%), were used for assessment of short- and intermediate-term exposures and risks, assuming, as a screening-level approach, continuous exposure to residues present immediately after application" (EPA, 2020). EPA also noted that a 4-day average transferable residue was estimated for short- and intermediate-term exposures using the results of the first order decay modeling and a 28-day average exposure was estimated using the same approach for long-term exposures but no FAR or daily dissipation were values were provided (EPA, 2020). However, it can be assumed that these longer averaging times produced FAR values that are lower than the 1.4% value from day 0.

DPR Response: In its 2020 assessment, US EPA used the same 4-day average values for both short- and intermediate-term exposures because "*the thyroid effects used to set the POD were identified in offspring on postnatal day 4 and there is evidence to suggest that the offspring were directly exposed to fipronil in milk during this period"* (US EPA, 2020). DPR used different POD values for short- and intermediate-term exposures in its draft and final Risk Characterization Document. Based on the selection of the POD value and DPR's definition of short-term exposure as provided in the response above to the Comment on Applicator scenarios as well as a previous DPR memo from Frank (2009), DPR used the

upper-bound exposure values, which could be either the estimated 95th percentile value or the maximum measured value, to estimate the short-term absorbed daily dose (STADDs).

As mentioned above, in the revised EAD, DPR used 7-day average dislodgeable fipronil residues on pets to estimate resident (adult and child) intermediate-term post-application exposures (SADDs). All the relevant texts and tables in section "IV. EXPOSURE ASSESSMENT" of the final EAD were revised accordingly. This is based on DPR's definition of intermediate-term exposure as "*periods of frequent exposures lasting greater than seven days to one year*" (Kwok, 2017). The method to estimate the 7-day average values was added to the final EAD for both pet spray and spot-on products. In general, the 7-day average was calculated using the highest measured dislodgeable residue within the first day after application (Day 0) and the estimated daily residues for the following 6 days from fitting the measured values (i.e., measurements at 8 hr, and Day 1, 2, 4 and 7) into a first-order decay model. The rationale of adopting this computational approach is due to the biphasic decrease of dislodgeable fipronil residue observed within the first seven days, with a much faster decrease in Day 0 than the following days.

Comments pertaining to the upper-bound values versus 95th percentile are addressed in the response to "Applicator: pet groomer and home user," above. DPR does not agree with the statement of "*assumptions used to calculate the exposure of at-risk persons push well beyond the 95th percentile and postulate a series of circumstances that may be individually plausible but collectively are implausible*" from the reviewers, as for short-term exposures, other than the upper-bound values for dislodgeable residues, all other parameter values (cat/dog size, surface area, contact time, etc.) used were determined based on survey studies and are recommended values by US EPA (2012).

Request for reconsideration - Exposure Assessment: Conclusions

FTF Comment: …[O]verall, the approach for estimating short-term exposures presented in the draft RCD lacks a scientific substantiation and is inconsistent in practice. The estimation of short-term exposures using consistent and plausible conservatisms as well as statistical methods that can be scientifically justified, which in this case should be the use of the maximum empirical values from the conducted studies that have built in conservatisms, is critical to conducting scientifically sound and regulatorily appropriate risk assessments.

DPR Response: Responses to individual FTF comments are presented above. For each assessed scenario, the equations to calculate short-term exposures and the supporting data to derive equation parameters have been presented in "IV. EXPOSURE ASSESSMENT" of the EAD. The rationale of selecting these data and how data gaps were addressed were also discussed in "V. EXPOSURE APPRAISAL" of the EAD. Conservative assumptions might be made, such as using upper-bound exposure estimates, when data gaps were encountered and to account for diverse fipronil use in California of a wide range of

products that may not be well-represented by limited number of studies and available data.

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