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OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

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Introduction

The Pesticide Re-evaluation Division (PRD) has requested that the Health Effects Division (HED) conduct an evaluation of comments received from the registrant, Mitsui Chemicals Agro, Inc. (MCAG) on the *"Human Health Draft Risk Assessment for Registration review and Proposed Section 3 Use on Fungi, Edible, Group 21 and All Food Commodities (Including Feed Commodities) as the Result of Mosquito Control" (D431867; EPA-HQ-OPP-2007-0804-0036).*

Comment #1. Model used for Inhalation Exposure Assessments

The registrant believes the inhalation exposure assessments could be refined by using an updated model for the human equivalent inhalation endpoint extrapolation. For human equivalent dose conversions (HEC) other divisions within EPA have used an updated model such as MPPD

(Multiple Pathway Particle Dosimetry) version 3.04 for inhalation assessments rather than the older RDDR model that was used for the etofenprox assessment. The extrapolation value from the MPPD model is 5.35 rather than the RDDR value of 2.52. This updated value would result in more than two-fold increase in the point of departure or acceptable threshold for inhalation route assessments.

HED Response: At this time, HED is not using the MPPD model in the risk assessment process. The validation and approval process is still underway and until that is complete HED will not apply it for conducting or refining risk assessments.

Comment #2. Inhalation Space Sprays

EPA used the CLS product, RF2162 Premium Aerosol (1.0% ai) (EPA Reg. No. 89459-10), as the model for indoor space spray exposure. It is not clear why the EPA chose this product to calculate space spray exposure. There are no space spray directions for use for this product. The registrant for this product, Central Garden & Pet (CGP), has indicated that common commercial pressurized aerosols currently marketed do not have space spray uses. Indoor uses for these products are restricted to crack and crevice, spot and broadcast surface sprays.

In addition to discussing the end-use products to be evaluated in the risk assessments, MCAG would like to discuss the models used in the assessment and possible mitigation measures such as ventilation before re-entry.

HED Response: At the time the HED assessment was conducted there were 11 registered etofenprox aerosol can products. The CLS product, RF2162 Premium Aerosol (1.0% ai) (EPA Reg. No. 89459-10), was used because it was the etofenprox aerosol product with the highest concentration or maximum application rate of the various etofenprox aerosol products currently registered. Upon further review of this product label, HED agrees that this product will not be used as a space spray. Additionally, upon further review of the other 10 registered etofenprox aerosol can products, HED has concluded that none of these products would be used as a space spray; and therefore, the assessment of inhalation exposure risk immediately after an aerosol is sprayed is not needed.

Comment #3. Indoor Residential Post-Application Non-Cancer Dermal & Incidental Oral Exposure and Risk Estimates

As with the indoor space spray assessment, EPA's risk assessment process for indoor residential uses was not entirely transparent. The registrant would like to discuss the models used and possible mitigation measures to refine the risk assessments.

HED Response: As noted in the Etofenprox Draft Risk Assessment (p. 37 of 77), the assessment of indoor residential uses followed HED's 2012 Residential SOPs[1]. These publicly-available SOPs provide guidance and information regarding the underlying assumptions for the indoor residential post-application exposure and risk assessments. Additionally, the algorithms

[1] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

used to calculate the risk estimates for the residential uses were included in Appendix A of the HED occupational and residential exposure assessment (D440307, B. O'Keefe, 06/26/2017; *Occupational and Residential Exposure Assessment for a Proposed Section 3 Use on Fungi, Edible, Group 21 and for Registration Review*).

Comment #4. Mushroom Houses

There is an error in EPA's assessment for the mixer/loader applicator for manually pressurized handwand and mechanically pressurized handgun. In Table 8.1.1, the unit exposure is reversed for the two scenarios. EPA concluded, based on PPE of a single layer plus gloves (SLG), that the manually pressurized handwand fails while the mechanically pressurized handgun passes. In fact, the opposite is true. In addition to the error in the unit exposure, MCAG believes the assumptions used in the assessments do not represent typical mushroom house practices.

The proposed application rate for mushroom houses is 1 gallon mixture/1,000 ft^2. A typical mushroom house room is 2,400 ft^2. Therefore, an applicator would need 2.4 gallons of mixture for each room. Using the EPA's assumptions for the mechanically pressurized handgun would be able to treat 22 acres of mushrooms per day using the mechanically pressurized handgun. This would lead to one individual being able to treat 416 rooms in one day with the mechanically pressurized handgun. In addition, the EPA assumed one individual will apply 40 gal/day using a manually pressurized handwand which would treat 17 rooms per day. MCAG believes that default amounts of 1,000 gal/day of product applied with a mechanically pressurized handgun and 40 gal/day applied by manually pressurized handwand are gross overestimates of the area that can be treated by one person in one day. Mushroom growers have confirmed values used by the EPA are not representative of industry practices.

Typical industry practice for a large mushroom grower is 2 growing rooms per day or 4.8 gallons of mixture in a single day. As noted above, the EPA assumptions allow for treatment of 416 growing rooms per day for a mechanically pressurized handgun and 17 growing rooms per day for a manually pressurized handwand which are both gross overestimates of the 2 growing rooms that can realistically be treated per day. In addition, most farms do not contain 416 rooms for treatment.

MCAG would like to discuss the input parameters for the mushroom house assessments and potential mitigation measures with the Agency.

The Mushroom Institute will confirm typical mushroom house practices in a separate letter to the Docket.

Another comment was received from the Western Integrated Pest Management (IPM) Center on the Draft Human Health and Ecological Risk Assessments for pyrethroids and certain other pesticides (EPA-HQ-OPP-2015-0393; including etofenprox). Part of the comment focused on the use pattern for mushrooms and reported that 70.88 acres and 21.01 lb of etofenprox where used on mushrooms in California in 2015.

HED Response: HED acknowledges that the risk estimates for the manually pressurized handwand and mechanically pressurized handgun scenarios were inadvertently switched. The risk estimates of concern are associated with the mechanically pressurized handgun and not with the manually pressurized handwand.

The HED default values of 1,000 gal/day for a mechanically pressurized handgun and 40 gal/day for a manually pressurized handwand are the standard units of the amount treated per day for these equipment scenarios in HED's occupational SOPs. These default units are based upon the fact that a contracted occupational handler can apply such amounts per day if they visit numerous sites. Without additional data or information to demonstrate that this would not occur, HED assumes that a handler could handle these amounts daily. If MCAG and/or the American Mushroom Institute can provide HED with survey data, or other data that are representative of the mushroom industry practices for occupational handlers then, upon review of these data, HED may consider refinements to the standard assumptions for the amount treated daily for these equipment scenarios in mushroom houses. Ideally this information would come in the form of survey data documenting individual mushroom house application event level and would include, but not necessarily limited to, the following fields of information:

- Technician identifier (not including any personally identifiable or employer/company information)
- Date of application
- Product (EPA Reg #)
- Application equipment (as specific as possible)
- % Concentration (if diluted)
- Amount applied in gallons of solution
- Area treated (square feet and/or cubic feet)

MCAG and/or the American Mushroom Institute can also present anecdotal information based upon their own knowledge regarding some of these fields in an informal fashion. For example, describe ranges (minimum, maximum, average) for amounts of solution applied and area treated *per application event* and then the potential for there to be multiple application events in a day for a contract applicator. As implied above by including a "date of application" field in a potential survey, information regarding application frequency (e.g., applications per week or month) can also help inform the risk assessment. As with any submission, please provide references, rationales, justification, etc. for the information provided.

Comment# 5. Inside Non-Food/ Non-Feed Areas of Residential, Noncommercial and Commercial Buildings, Industrial Buildings, Storage Facilities and Transport Containers

Treatment of food handling establishments, warehouses, residential living spaces, and childcare centers resulted in unacceptable risk. The risk calculations were done using EPA Reg. No. 86203-5 which has a much higher application rate than the commercially available product (EPA Reg. No. 2724-804). The risk for EPA Reg. No. 2724-804 is acceptable with single layer gloves using a manually pressurized handwand and applying 40 gal/day. The EPA assumed one person could apply 1000 gal/day using a mechanically pressurized handgun. The registrant does not believe the value of 1000 gal/day is representative of industry practices. Pest management users

have indicated the maximum amount applied per day per individual is 2 gallons/40,000 square feet of warehouse space, while applications with a mechanically pressurized handgun are not typical industry practice in these facilities.

Broadcast applications are not made to large expanses of floor space. Typical applications are crack and crevice and spot treatments. If an applicator were to apply 40 gallons a day using a manually pressurized handwand sprayer, the applicator will treat approximately 800,000 sq. ft. of warehouse space. Since it takes approximately 1 hour to treat 40,000 sq. ft. as a crack and crevice or spot application, treating 800,000 sq. ft. would take 20 man hours or about 2.5 days. The assumption that an individual will apply 40 gallons in one day is unrealistic and not typical of industry practices.

MCAG would like to discuss lowering the rate of EPA Reg. No. 86203-5, the input parameters used in the assessments and potential mitigation measures in order to refine the assessments.

HED Response: HED conducts risk assessments using registered end-use products for the purposes of Registration Review. Therefore, risk calculations were done using EPA Reg. No. 86203-5, a registered etofenprox product that has the highest application rate for this particular use pattern scenario. HED agrees that lowering the application rate for EPA Reg. No. 86203-5 would lower the occupational handler risk estimate.

The HED defaults of 1,000 gal/day for a mechanically pressurized handgun and 40 gal/day for a manually pressurized handwand are the standard units of the amount treated per day for these equipment scenarios in HED's occupational SOPs. These default units are based upon the fact that a contracted handler can apply such amounts per day if they visit numerous sites. Without additional data or information to demonstrate that this would not occur, HED assumes that a handler could handle these amounts daily. If MCAG can provide HED with survey data, or other data concerning the amount treated per day by a handler using a mechanically pressurized handgun sprayer, or a manually pressurized handwand sprayer, then HED would consider reevaluating the daily amount handled assumptions.

Comment #6. Mosquito Adulticide Control

The truck mounted fogger applicator scenario resulted in unacceptable risk with single or double layer gloves and was acceptable only when head protection is worn. EPA used data from the agricultural open-cab airblast scenario when conducting the assessments for the mosquito ground application. It has been confirmed with the mosquito control industry that the open cab application scenario is not representative of practices used by mosquito abatement districts when applying mosquito adulticides or larvicides by truck-mounted ULV methods. Applicators apply products from trucks in air-conditioned cabs with the windows rolled up, thus essentially eliminating any exposure to etofenprox during application.

I. Applications for ground ULV fogging at 3,000 acres a day

The EPA's assumption of applying etofenprox at 3,000 acres a day via ground ULV is an overestimation of the actual acreage that can be applied per day. Polls from small and large AMCA member districts have provided information that average acres treated per

day is 174; therefore, the assumption from EPA of 3,000 acres is 17x higher than typical practices.

II. Use of an airblast applicator as a surrogate for traditional ground ULV equipment

The use of an airblast applicator is as a surrogate for traditional ground ULV equipment another does not represent typical practices. While there are some members that do use airblast applications, the majority use traditional cold aerosol generators manufactured by companies such as London Fog and Clarke. AMCA membership recommends that in order to provide an appropriate risk assessment, the actual equipment used in traditional fogging activities should be used in the calculation instead of an agricultural type applicator.

MCAG would like to discuss the scenarios used for the mosquito adulticide control uses and typical industry practices with the Agency.

The American Mosquito Control Association (AMCA) will be submitting comments to the Docket on standard industry practices.

HED Response: HED uses the airblast applicator scenario as a surrogate for the truck-mounted ground fogger because it is the best available data. As part of MCAG's comment, they acknowledge that some applicators use airblast applications. While airblast application may be a less popular method, compared to fogger units, EPA will continue to assess it so long as it remains a viable method. Also, without any real-world exposure data for applicators using truck-mounted ground foggers, HED will continue to rely upon this surrogate data. Concerning applicators being in enclosed cabs, HED does provide risk estimates for the enclosed cab scenario in the handler spreadsheet that accompanied the draft HED risk assessment document, although those risk estimates were not included in the risk assessment document. The combined dermal and inhalation risk for the enclosed cab scenario result in an aggregate risk index of 58, which is a risk estimate not of concern.

The assumption of 3,000 acres treated per day is the standard assumption used by HED in assessing mosquito adulticides. HED welcomes discussions with MCAG regarding etofenprox-specific acreage treated data or information, as well as additional comments regarding standard industry practices for mosquito adulticide control.

Comment #7. Pet Shampoo

The professional pet shampoo scenario fails with an ARI of 0.9 with or without gloves. When conducting the professional pet shampoo risk assessments, the EPA used the highest weight of dogs on the label (150 lbs.) as the default value. The default amount handled for this scenario is based on treating 8 dogs per day with an average dog weight of 150 pounds. These are very large dogs, and it is highly unlikely one handler will wash 8 dogs a day that are an average of 150 pounds. It should also be noted that this is a short-term assessment and it is especially unlikely a handler will have 30 days of exposure to eight 150 lb. dogs per day. A number of pet

groomers were surveyed and indicated a typical groomer washes approximately 8 dogs per day weighing an average of 62 pounds.

MCAG would like to discuss the scenarios used for the pet shampoo assessments and typical industry practices with the Agency.

HED Response: HED believes that the risk estimate using a 150 lb dog is a conservative, but reasonable estimate. EPA is open to information provided by MCAG that would invalidate this assumption, such as survey data or label information (e.g., restrictions on product use based upon the number/weight of treated dogs). With such additional information, HED is willing to consider its impact on the risk estimate.

Comment #8. Thyroid Mode of Action – Human Relevance for Assessing Thyroid Toxicity

I. Background

In 2001, HED requested a developmental neurotoxicity (DNT) study be conducted. The DNT was conducted and submitted by MCAG in 2003.

In June 2017, HED (DP Barcode D431867, D432256) requested that a Comparative Thyroid Assay (CTA) be conducted based on concerns that the anti-thyroid activity of etofenprox could lead to potential adverse effects in developing fetuses and neonatal pups.

The mode of action (MOA) of etofenprox resulting in the disruption of the thyroid hormones has been established and accepted by the agency to be the result of high levels of etofenprox causing an increase in hepatic induction of UDP-glucuronosyltransferase (UDP-GT) activity resulting in the conjugation of T4 and subsequent elimination of the T4 through fecal excretion. Hepatic induction was independently confirmed by Hojo et al (2012). Thyroid peroxidase activity was unaffected. Thus, the MOA is mediated by removal of T4 via conjugation and subsequent elimination with no direct impact on thyroid hormone metabolism/activation. The effect in the thyroid is secondary to high doses of xenobiotic that induce the liver enzyme UDP-GT. This MOA has little if any relevance to humans, particularly at the exposure levels anticipated.

In human fetuses, infants and children, thyroid dysfunction almost exclusively affects the central nervous system. Neurodevelopmental problems can result. It is manifested in defects of hearing and speech, disorders of stance and gait, stunted growth, mental deficiency, motor activity, neuropsychological skills, and sexual immaturity. Clinically there are three basic causes of these defects in the human population: iodine deficiency, autoimmune responses and congenital defects in the thyroid. Severely altered thyroid function in pregnant women generally results in miscarriage (Lazarus, 2007).

In the agency's 2005 Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals and Adult Animals, the concern was that exposure to a chemical shown to perturb thyroid hormone homeostasis via reduction of circulating thyroid hormones could result in neurological disorders and alterations in neurological development. The comparative thyroid assay was seen as an alternative to the more complex Developmental Neurotoxicity Assay

(DNT). Since that time, the agency has relied on the CTA as an indicator of susceptibility to thyroid active chemicals which measures T4, T3 and TSH. These blood chemistry measurements are an initial or concurrent indicator of the adverse biological effects caused by thyroid disruption. However, the definitive study for fetal and pup susceptibility to thyroid disruption remains the DNT as it measures the biological effects of thyroid enzyme disruption directly without reliance on the preliminary biochemical indicators.

Therefore, based on the questionable relevance to the human population and the results of a DNT showing no increased susceptibility of the pup to the adult, MCAG believes that the CTA is not necessary to understand the role of etofenprox in human neurological development and results of a CTA will not refine the current risk assessments. The 2-generation reproduction study, which also evaluated pregnant dams with two litters of F1 and two litters of F2 generations, has shown no enhanced sensitivity to offspring.

II. Thyroid Mode of Action of Etofenprox

In the rat, hepatic metabolism of thyroid hormone is well understood and accepted by the Agency. Generally, thyroxin (T4) is glucuronidated by UGTs and T3 is sulfated by phenol sulfotransferases. Conjugates of both hormones are subsequently excreted in bile. For T4, glucuronidation is the rate-limiting step in the biliary excretion. This results in a marked decrease in serum concentrations of T4 due to a shorter half-life. The decrease in T4 in turn leads to, via a feedback mechanism, increased levels of TSH. Increased TSH levels re-establish the thyroid hormone homeostasis. These increased TSH levels lead to an increased production (synthesis) of T4 to compensate for the shorter half-life induced by treatment. Differences in the thyroid between the rat and human make this mode of action not relevant to humans.

a. Human Relevance

Although both rats and humans have similar thyroid hormones and thyroid regulatory controls, there are many functional differences as documented by EPA (Hill et al, 1998) shown below. There are also species differences in basic hormone synthesis, basal TSH levels, metabolism and alterations to binding proteins during pregnancy (Choksi, 2003).

Parameter	Human	Rat
Half-life of T4	5-9 days	0.5 – 1 day
Half-life of T3	1 day	0.25 day
Thyroxine-binding globulin levels	High	Very low/not present
Amount of T4 required in absence of function thyroid gland	2.2 ug/kg bw/day	20 ug/kg bw/day
T4 production (rate/kg bw)	1X	10X
Sex differences in serum TSH levels	No difference	Adult males have higher levels than adult females
Follicular cell morphology	Low cuboidal	Cuboidal
Follicular height is equal in males and females		Follicular height in males is greater than in females

There are two basic factors that need to be considered. The rat and human have very different levels of free and bound T3 and T4 that are subject to conjugation by liver enzymes, and the human will deconjugate T4 in the gut and reabsorb the free T4, which does not happen as readily

in the rat. There is a high degree of thyroid hormone economy in the human system. Therefore, the MOA based on the induction of UDP-GT which conjugates and removes T4 leading to increased TSH levels in the rat, has little toxicological relevance to humans. These two factors lead to the radically different half-lives of T4 in rats and humans as shown above.

1. Free and bound thyroxin:

Thyroxin (T4) and triiodothyronine (T3) are transported in the blood as noncovalent complexes with certain serum proteins. These binding proteins are an a-globulin (called thyroxin-binding globulin or TBG), a prealbumin (TTR) and serum albumin. (Tritsch et al 1961). It is the free rather than bound T4 that is subject to homeostatic control by the hypothalamic-pituitary thyroid axis.

Human: Thyroxine travels in the blood attached to carrier proteins (primarily to thyroxine-binding globulin, or TBG). The thyroid also secretes a small amount of triiodothyronine, or T3 (most T3 is made from T4). The carrier proteins have a higher affinity for T4 than for T3, however, and, as a result, the amount of unbound (or "free") T3 in the plasma is about ten times greater than the amount of free T4. Approximately 99.96% of the thyroxine in the human blood is attached to carrier proteins in the plasma; the rest is free. See Table 1.

Table 1: Plasma proteins involved in thyroid hormone transport:

Protein	Conc (mg/dl)	K_a for T_4	%T_4 Bound	K_a for T_3	%T_3 Bound
TBG	1.5	10^{10}	75	10^{9}	70
TBPA	25.0	10^{7}	15	10^{6}	----
Albumin	4000.0	10^{6}	10	10^{5}	30

* TBPA = TTR
Taken from DeRuiter http://www.duc.auburn.edu/~deruija/endo_thyroidintro.pdf

The percentage of unbound T4 is lower in species with high levels of TBG than in animals (rats) in which T4 binding is limited to albumin and prealbumin. Only the free thyroxine (and T3) can enter target cells; the protein-bound thyroxine serves as a reservoir of this hormone in the blood. Once the free thyroxine passes into the target cell cytoplasm, it is enzymatically converted into the active T3 by deiodinases. It is the T3 rather than T4 that is active within the target cells. T3 is three to four times more potent than T4 but T4 is nearly 4 times more prevalent than T3.

Bound T4 will not be available for conjugation by induced liver enzymes. Because the binding affinity of TGB is four orders of magnitude greater than that of albumin, T4 in humans (bound to TBG) is not as available as it is in the rat (bound to albumin).

Rat: In contrast to the human biochemistry, rat T4 and T3 is bound primarily by prealbumin and albumin (see Table 2). The rat does not have thyroxine-binding globulin (TBG). The percentage of unbound active T4 is lower in species with high levels of TBG than in animals in which T4 binding is limited to albumin and prealbumin. A rat without a functional thyroid requires about 10 times more T4 for full substitution than an adult human. In general, T3 is bound less avidly to transport proteins than T4 resulting in a faster turn-over and shorter plasma half-life in most species.

Treatment with UDP-GT inducers significantly reduces free T4 in the rodent. (Liu et al, 1995) It is not as likely to affect human T4 that is tightly bound to TBG.

Mouse: It is of interest to note that in the mouse there is a heavy reliance on post albumin. This is more similar to the 'postalbumin' TBG found in humans. It is also interesting to note that although the mouse liver can be induced to produce exogenous xenobiotic metabolizing enzymes, there is no etofenprox effect on the thyroid in mice. The effects observed in mice with respect to liver enzyme inducers are in the liver.

The activation of the thyroid gland during the treatment of rodents with substances that stimulate thyroxine catabolism is a well-known phenomenon and has been investigated extensively with phenobarbital and many other compounds. It occurs particularly in rodents, first because UDP-GT can easily be induced in rodent species and second because thyroxine metabolism takes place very rapidly in rats in the absence of thyroxin-binding globulin. In humans, a lowering of the circulating T4 level, but no change in TSH and T3 concentrations, has been observed only with high doses of very powerful enzyme-inducing compounds such as rifampicin with and without antipyrine (Capen, 1997). UDP-GT inducers can adversely affect the thyroid gland by a secondary mechanism, but this only applies to those UDP-GT inducers that increase serum TSH in addition to reducing serum T4 (Capen, 1997). TSH in humans has not been shown to increase in response to UDP-GT induction.

Phenobarbitol, the most studied inducer of the liver xenobiotic metabolizing system, will increase biliary excretion with an elevated TSH which allows for the maintenance of normal thyroid function (McCain, 1989). In humans, phenobarbital did not affect serum T4, T3 or TSH levels (Ohnhaus et al 1981). Phenobarbital only in combination with rifampicin or antipyrine was a strong enough enzyme inducer to affect human T4 levels, however there was no effect on serum T3 or TSH (Ohnhaus and Studer, 1983). It is highly unlikely that the very weak etofenprox induction of phase I and Phase II enzymes would be potent enough to affect the human thyroid levels.

Table 2. T4 binding to serum proteins in selected vertebrate species.

Species	TBG*	Postalbumin	Albumin	Prealbumin**
Human	++	--	++	++
Monkey	++	--	++	++
Dog	+	--	++	--
Mouse	--	++	++	--
Rat	--	+	++	++
Chicken	--	--	++	--

Why are these species differences important? If there is not free T4 in the liver, the UDP-GT enzyme will not be able to catabolize the T4 resulting in the feedback mechanism leading to increased TSH. The levels of T4 in humans will not be reduced by the increase in UDP-GT concentrations induced by etofenprox. The combination of the differences in binding capabilities of T4 to TBG and albumin as well as the differences in free and bound T4 results in a half-life of plasma T4 of 12 – 24 hours in the rat versus 5 – 9 days in the human. These differences in plasma half-life of thyroid hormones and binding to transport proteins between

rats and humans is one factor in the greater sensitivity of the rat thyroid to developing a chronic TSH stimulation.

2. Reabsorption of eliminated conjugated T4

It is well known that in man, conjugated T4 excreted in the bile is readily deconjugated and reabsorbed by the gut as free T4. Thus, in the human system, T4 is reclaimed. The gut plays a major role as a reservoir for the thyroid hormones whether conjugated or free in contrast to the rat. Absorption appears to be reduced in the presence of excess T4 and increased in hypothyroidism or decreased T4 levels (Hays, 1988).

In the rat, it is known that the conjugated T4 will be excreted through the bile or urine and that with increased conjugation (induced by polychlorinated biphenyls or phenobarbital) results in increased elimination of T4 leading to a hypothyroid state. Treatment with these chemicals also appeared to reduce the binding of serum proteins to thyroid hormones in the rat. Half of eliminated T4 is through the feces via the bile (Distefano, 1988). The rest is either completely degraded or excreted via the urine (not reclaimed). Little conjugated thyroid hormone is absorbed from the gut into the blood.

Overall: It is the combination of these two major differences between rodents and man that results in a substantial difference in the half-life of T4. Human T4 is more resistant to fluctuations in liver xenobiotic metabolizing enzymes.

b. Clinical Outcomes of Thyroid Dysfunction in Humans

In human fetuses, infants and children, thyroid disfunction almost exclusively affects the central nervous system. Neurodevelopmental problems can result. These are manifested as defects of hearing and speech, disorders of stance and gait, stunted growth, mental deficiency, hypothyroidism and sexual immaturity. This condition has been termed cretinism (Knobel, Medeiros-Neto, 2007). These effects are primarily observed in conjunction with iodine deficiency. Autoimmune disorders of the thyroid (Weetman, 2007) are also a cause of thyroid disease in children. Congenital Hypothyroidism (CH) or genetic defects of thyroid hormone synthesis (Karges, 2007) are characterized by low birth weight, short stature and pubertal development along with deficits in visual, language, motor, attention and memory abilities. Whether hypothyroid or hyperthyroid, the clinical effect is poor growth, auditory, visual and neuropsychological skills.

III. Etofenprox Toxicity

Several studies have been conducted that allow evaluation of the thyroid effects in adult animals, pregnant animals, fetuses and postnatal animals. The chronic/carcinogenicity study provides an understanding of the weak liver and thyroid effects observed in adult animals. The reproduction and fertility study provided data on the potential susceptibility of the offspring through two generations. There was no evidence of increased susceptibility in the offspring. Although thyroid hormones were not measured in this study, thyroid effects (thyroid weight increase and hypertrophy) in the offspring were seen at the same dose that caused parental thyroid toxicity.

This indicates that there is no potential for thyroid disruption in the young at lower doses. In the developmental neurotoxicity study, there was no evidence for adverse effects on the development of the fetal nervous system, brain weight or brain morphometrics in the offspring at any dose level. Lack of these effects is another indicator that etofenprox does not cause adverse effects in the young. None of these studies give any indication that the offspring are more adversely affected by the induction of liver enzymes leading to the secondary changes in thyroid hormones.

IV. Agency's Request for Comparative Thyroid Assay

In the 2005, the agency issued a "Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals and Adult Animals" to generate thyroid specific data at various life-stages when a chemical perturbs thyroid hormone homeostasis via reduction of circulating thyroid hormones which could result in neurological disorders and alterations in neurological development. The guidance states:

"Normally, if a neurodevelopmental concern is raised by existing data on a pesticide, a rat developmental neurotoxicity (DNT) study is requested. However, disruption of thyroid homeostasis by thyroid disrupting pesticides is the initial, critical effect that may lead to adverse effects on the developing nervous system. Thus, in lieu of the rat DNT study, the special study described herein entails a mechanistic approach to generate specific data on the thyroid (i.e., the primary target of the chemical of interest) to protect the developing nervous system from thyroid hormone disrupting chemicals."

Based on the 2005 guidance, the agency has required a CTA for etofenprox to address the potential for thyroid effects in the fetuses and/or neonate. However, the DNT study addressed this concern by evaluating the effect of etofenprox directly on the neurological system. The DNT addressed the biological effect rather than the preliminary effect of altered thyroid hormones as measured by the CTA.

V. Conclusion:

It is well documented that rats are more susceptible to thyroid disrupting chemicals than humans and the rat is more sensitive to hypothyroidism than human. The MOA studies have demonstrated that etofenprox thyroid toxicity is mediated through the liver. There was no evidence of increased susceptibility in the offspring either in the two-generation reproduction study or in the DNT study.

Etofenprox did not affect neurological function or brain weight or changes in brain morphometry of the rat offspring.

Since the disruption of thyroid in the pregnant woman results in neurological effects in infants and children, it is the neurological endpoints that are relevant in the rat for a direct species comparison. We know that the rat is more sensitive than the human to thyroid disruption and thyroid effects. Therefore, if neurological effects are not observed in the rat, they will not be manifested to a greater extent in the human, they will be much weaker. More importantly, the

MOA for thyroid disruption in the rat is not relevant to the human population. It is a logical conclusion that if the effects in the adult rat are not to relevant to the human adult, the effects in the rat pup will not be relevant to the human infant or child.

Interpretation of hormone results in the CTA study will be difficult. Neonates have very different thyroid levels and TSH than the adults and the ratios of T4, T3 and TSH fluctuate as the animal matures (Szabo et al, 2009). These hormones fluctuate in the pregnant rat dam as well as in the pregnant woman and developing human fetus and infant (Spiliotis, 2007). The measurements of T4, T3 and TSH have their own intrinsic variability. Therefore, because of the slight effect of etofenprox on thyroid hormones in adults, it will be very difficult to interpret data that will have small effects in a background of high variability.

The CTA study utilizes large numbers of animals (approximately 2,000). In addition, since the MOA of etofenprox has little human relevance, there is an accepted DNT study for etofenprox, and all data indicate that there are no differential effects on offspring, the registrant needs to understand how the results of the CTA study will provide additional information to understand the toxicity of etofenprox, refine the risk assessments or inform regulatory decisions that the EPA cannot already elucidate from the current database.

MCAG would like to discuss the requirement of the CTA with the EPA to better understand how the study will determine toxicity and how the results will be used to refine the risk assessments or inform regulatory decisions.

HED Response: The FQPA (1996) instructs the EPA that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." While there was no evidence of prenatal or postnatal susceptibility in the available database, disruption of thyroid function in fetuses and juveniles can lead to alterations in neurological development. Therefore, the EPA considers the perturbation of thyroid hormone homeostasis to be an adverse effect. However, the current guideline studies do not include measurements of thyroid hormones during early lifestages. In this light, the purpose of the comparative thyroid assay (CTA) is to generate data to establish points of departure that are protective of the ability of a chemical to disrupt thyroid function in pregnant females, fetuses, and newborns. Currently, OPP is developing a weight of evidence (WOE) framework for evaluating the need for a CTA that considers both hazard and exposure.

The EPA appreciates the thoughtful and thorough presentation on the thyroid mode of action and its human relevance for assessing thyroid toxicity as presented by the registrant. The Agency notes that the science and data presented pertain to adults. The extent to which these data correlate with the young, either in rats or humans, has not been established. As such, uncertainties regarding relative toxicity of etofenprox in the young remain. Therefore, a CTA is required for etofenprox.