UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

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Subject: **Metofluthrin.** Occupational and Residential Exposure Assessment for a Proposed Use in an Outdoor Area Repellent

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Introduction

The Registration Division (RD) requested that the Health Effects Division (HED) conduct an exposure and risk assessment for a proposed new product called FAN, which is a battery operated area repellent containing the insecticide metofluthrin. No risks of concern were identified in this assessment, and therefore HED has no objection to the registration of the proposed new product.

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1.0 Executive Summary

The Registration Division (RD) requested that the Health Effects Division (HED) conduct an exposure and risk assessment for a proposed new product called FAN, a battery operated area repellent containing the pyrethroid insecticide metofluthrin. The solvent based formula will be packaged in a pressurized can and sold with a plastic shroud capable of releasing metered doses of repellent for preset time intervals up to 3 hours.

Besides the proposed use, metofluthrin has a number of currently registered products including impregnated paper repellent strips, a personal outdoor insect repellent fan, and a recently registered candle product. There are no food/feed uses and no drinking water exposure is expected from the repellent uses (including the proposed use pattern). HED completed a human health risk assessment for a new use request to control bed bugs and to support registration review in September, 2012. That assessment also served as a preliminary risk assessment to support registration review in that HED prepared revised residential handler and post-application assessments for metofluthrin for the currently registered uses in mosquito repellent products (including a recently registered candle product) to reflect the Revised Residential SOPs (2012). No risks of concern were identified in this assessment; and the exposure scenarios assessed in this document result in lower risk estimates (i.e., higher calculated MOEs and ARIs) than the other scenarios assessed in the 2012 human health risk assessment.

Hazard Profile and Points of Departure (POD)

Metofluthrin is a Type I pyrethroid, and like other pyrethroids, causes neurotoxicity from interaction with sodium channels leading to clinical signs of neurotoxicity. Following a single oral gavage dose, metofluthrin is absorbed quickly in rats. Neurotoxicity is observed within 6 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect. The no-observed-adverse-effects-levels (NOAELs) and lowest-observed-adverse-effects-levels (LOAELs) established from metofluthrin single dose and repeat dosing studies show that repeat exposures do not result in lower NOAELs (i.e. increasing toxicity). Thus, for purpose of endpoint selection and exposure assessment, only single day risk assessments need to be conducted.

A 90-day dermal toxicity study in the rat was selected for use in assessment of short- and intermediate-term dermal exposures. The NOAEL was 300 mg/kg/day based on mortality and clinical signs of toxicity including tremors and salivation observed at the LOAEL of 1000 mg/kg/day. The dermal study is protective of potential offspring effects since it adequately measured systemic toxicity in adult animals, and there were no developmental or offspring effects that were not evaluated in the dermal study.

The maternal effects from the rat developmental toxicity study were selected for the assessment of short-term incidental oral exposure. The maternal NOAEL of 15 mg/kg/day, based on tremors at the high dose of 30 mg/kg/day, was the most sensitive endpoint for oral exposure for short-term duration. The NOAEL and endpoint from the selected study are protective of potential developmental effects including offspring effects in the rat reproduction study which occurred at a higher dose (NOAEL/LOAEL = 97.6/183.6 mg/kg/day).

A 28-day inhalation toxicity study in the rat was selected for use in assessment of short- and intermediate-term inhalation exposures. The NOAEL was 0.099 mg/L (7.5 mg/kg/day for residential exposure) based on tremors, clinical signs and mortality, observed at the dose of 0.196 mg/L. The inhalation study is protective of potential offspring effects since it adequately measured systemic toxicity in adult animals, and the developmental and reproduction studies did not identify effects that were not evaluated in the inhalation study. In order to assess exposure via the inhalation route, the reference concentration methodology developed by the Office or Research and Development (ORD) was used to determine human equivalent concentrations (HECs) and human equivalent doses (HEDs) for risk assessment.

In order to assess exposure and risk, HED used the default body weight of 11 kg for children and the average adult body weight of 80 kg, given that the endpoints chosen for risk assessment were not sex-specific.

Metofluthrin is classified as 'Not likely to be carcinogenic to humans at doses that do not result in a mitogenic response'. Genotoxicity studies were negative. The doses selected for risk assessment are protective of potential carcinogenic effects.

Food Quality Protection Act (FQPA) considerations do not apply to metofluthrin for the proposed and existing (non-food) use patterns. However, since metofluthrin is a pyrethroid and exposure to children under <6 years old is expected, the Agency has retained a 3X uncertainty factor (UF), based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics.

For dermal residential and occupational scenarios involving adults, the level of concern (LOC) is a Margin of Exposure (MOE) of 100, based on the 10X uncertainty factors to account for interspecies extrapolation and intraspecies variability. For dermal and incidental oral exposure to children <6 years old, the additional 3X UF to account for potential sensitivity in the young results in LOCs of 300 for both the incidental oral and dermal exposure routes. Therefore, risk estimates (MOEs) above the respective LOCs for adults or children indicate risk estimates are not of concern.

For residential inhalation scenarios involving adults, the level of concern (LOC) is a Margin of Exposure (MOE) of 30, based on a 3X uncertainty factor to account for interspecies extrapolation (reduced from 10X because the HEC calculation accounts for pharmacokinetic differences between humans and rats) and a 10X uncertainty factor for intraspecies variability. For children <6 years old, the LOC is 100. Risk estimates (MOEs) above the respective inhalation LOCs for adults and children indicate risk estimates are not of concern.

Although the endpoints selected for incidental oral, dermal and inhalation routes of exposure are similar (i.e., tremors and clinical signs), the dermal and incidental oral routes have different LOCs than the inhalation route. Therefore, in order to combine exposure from the various routes the aggregate risk index (ARI) approach is used to estimate risk. ARIs ≥ 1 are not of concern.

<u>Residential Handler Exposure and Risk</u>

FAN Area Repellent Use: The metofluthrin-based product FAN does not require a residential handler assessment as handler exposure is expected to be negligible.

Residential Post-application Exposure and Risk

There is the potential for post-application exposure for individuals exposed as a result of being in outdoors areas after the metofluthrin-based FAN product has been deployed. The ARI estimate for adult post-application exposure (inhalation and dermal) is 240 and the ARI estimate for children's post-application exposure (inhalation, dermal, and incidental oral) is 27. Since the ARI's for adults and children for the combined exposure routes are above 1, no risk estimates of concern have been identified in this assessment.

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include the Residential SOPs (Section 5: Outdoor Fogging and Misting Systems)**;** are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[1].

2.0 Risk Assessment Conclusions and Recommendations

Short-term risk estimates for the residential post-application assessment exceed HED's level of concern (i.e., MOEs > LOC for all lifestages assessed and the ARI>1) for the scenarios/exposure routes assessed. No quantitative assessment was conducted for the occupational exposure scenarios (handler or post-application) because this metofluthrin-based repellent is designed and intended to be marketed for the consumer market.

The acute toxicity classification for primary eye irritation of metofluthrin is Category IV for primary eye and skin irritation. The acute toxicity classification for acute oral, dermal, and inhalation are all Category III. At this time, no additional information is needed to refine this assessment.

3.0 Hazard Characterization

HED completed a human health risk assessment for metofluthrin that evaluated a proposed use as well as the existing residential use patterns in September, 2012[2]. Before completing this action, HED evaluated the toxicological database for metofluthrin and no new studies or information are available that would impact the hazard characterization and dose-response assessment identified in that risk assessment.

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[1] http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html

[2] **Metofluthrin.** Human Health Risk Assessment for the New Use to Control Bed Bugs and to Support Registration Review (D402777, D403390)

3.1 Hazard Profile

Metofluthrin is a Type I pyrethroid, and like other pyrethroids, causes neurotoxicity from interaction with sodium channels leading to clinical signs of neurotoxicity. One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, metofluthrin is absorbed quickly in rats. Neurotoxicity is observed within 6 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect. The NOAELs and LOAELs established from metofluthrin single dose and repeat dosing studies show that repeat exposures do not result in lower NOAELs. Thus, for purposes of endpoint selection and exposure assessment, only single day risk assessments need to be conducted.

Technical metofluthrin has low acute oral, dermal, and inhalation toxicity (Toxicity Categories III). It is not a dermal or eye irritant (Toxicity Category IV) and is not a dermal sensitizer.

A 90-day dermal toxicity study in the rat was available and was selected for use in assessment of short- and intermediate-term dermal exposures. The NOAEL was 300 mg/kg/day. Significant findings at the LOAEL of 1000 mg/kg/day included tremors, which were also observed at the LOAEL of the critical study selected for incidental oral exposure assessment (rat developmental study). Mortality was also observed at 1000 mg/kg/day. The developmental toxicity and reproduction studies were also considered for dermal risk assessment. However, no developmental effects were noted in the developmental studies and the offspring effects in the reproduction study were seen in the presence of comparable maternal effects; therefore, there is no concern for increased susceptibility. The dermal study is protective of potential offspring effects since it adequately measured systemic toxicity in adult animals, and the developmental and reproduction studies did not identify effects that were not evaluated in the dermal study. Since the dermal endpoint was based on a dermal study, a separate dermal absorption factor was not required for estimating dermal exposure.

The maternal effects from the rat developmental toxicity study were selected for the assessment of short-term incidental oral exposure. The maternal NOAEL of 15 mg/kg/day, based on tremors observed at the high dose of 30 mg/kg/day, was the most sensitive endpoint for oral exposure for short-term duration. Comparable but slightly higher NOAELs were observed in the rat 90-day and six-month dietary studies (17-22 mg/kg/day), based on hepatotoxicity and body weight decreases at 54 -73 mg/kg/day. The NOAEL and endpoint from the selected study are protective of potential developmental effects including offspring effects in the rat reproduction study at a higher dose (NOAEL/LOAEL = 97.6/183.6 mg/kg/day).

A 28-day inhalation toxicity study in the rat was selected for use in assessment of short- and intermediate-term inhalation exposures. The NOAEL was 0.099 mg/L (7.5 mg/kg/day) was based on tremors at the LOAEL of 0.196 mg/L. Tremors, which were also observed at the LOAEL of the critical study selected for incidental oral exposure assessment (rat developmental study), and other neurological clinical signs. A high rate of mortality was also observed. The

developmental toxicity and reproduction studies were also considered for inhalation risk assessment. However, no developmental effects were noted in the developmental studies and the offspring effects in the reproduction study were seen in the presence of comparable maternal effects; therefore, there is no concern for increased susceptibility. The inhalation study is protective of potential offspring effects since it adequately measured systemic toxicity in adult animals, and the developmental and reproduction studies did not identify effects that were not evaluated in the inhalation study.

For purposes of estimating inhalation risk resulting from occupational and residential exposure, a human equivalent concentration (HEC) and human equivalent dose (HED) were derived in accordance with standard methodology that results in a reduction in the interspecies uncertainty factor (UF) from 10X to 3X. The HED determined for occupational inhalation risk assessment is 7.4 mg/kg/day; for residential risk assessment, the HED is 7.5 mg/kg/day.

For exposure and risk assessment, HED assumed a body weight of 11 kg for children; given that the endpoints chosen for risk assessment were not sex-specific, HED has used the average body weight of 80 kg for adults.

Metofluthrin is classified as 'Not likely to be carcinogenic to humans at doses that do not result in a mitogenic response' (Metofluthrin: Second Report of the Cancer Assessment Review Committee, TXR No. 0054668, July 26, 2007). The classification was based on an increased incidence of liver adenomas and carcinomas in both sexes of Wistar rat with supporting mechanistic studies demonstrating a mitogenic mode of action based on induction of liver cytochrome p450, resulting in a proliferative (mitogenic) response and eventual tumor formation. Genotoxicity studies were negative. The doses selected for risk assessment are protective of potential carcinogenic effects.

3.2 FQPA and Uncertainty Factor

Food Quality Protection Act (FQPA) considerations do not apply to metofluthrin for the existing and proposed (non-food) use patterns described in this risk assessment. However, since metofluthrin is a pyrethroid and exposure to children under <6 years old is expected, metofluthrin must be considered in the greater context of the pyrethroids as a class. The Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics and the applicability of these findings to all pyrethroids. This is consistent with the Agency's 2011 analysis and is supported by rat PBPK model predictions of a 3-fold increase of deltamethrin concentrations in the juvenile brain compared to adults. The PK of pyrethroids as a group is sufficiently similar that significant deviations from the 3-fold increase of deltamethrin concentrations are not expected for other pyrethroids. Juveniles are not more sensitive than adults with respect to pyrethroid pharmacodynamics and thus no uncertainty factor is needed for PD considerations.

Exposure from incidental oral, dermal and inhalation routes are based on different and route-specific studies, but similar endpoints all relevant to the sodium channel interaction of metofluthrin (i.e., clinical signs including tremors) were identified in each case. Occupational

and residential exposures from these routes may therefore be combined. Based on the traditional uncertainty factors of 10X for intraspecies variability and interspecies extrapolation, along with the additional 3X uncertainty factor to protect for exposures to children (<6 years of age), the level of concern (LOC) for children's dermal and oral risk is an MOE of 300. The LOC for adult dermal risk is an MOE of 100, based on the traditional 10X UFs for intraspecies variability and interspecies extrapolation. However in the case of inhalation risk, the interspecies uncertainty factor was reduced from 10X to 3X because the HEC calculation accounts for pharmacokinetic (not pharmacodynamic) interspecies differences between animals and humans. Therefore, the inhalation LOC is an MOE of 30 for the adult population and is an MOE of 100 for children < 6 years old. MOEs greater than the LOC are not of concern.

Although the incidental oral, dermal and inhalation routes of exposure have similar toxic effects (i.e., tremors), the dermal and incidental oral routes have different LOCs than the inhalation route. Therefore, in order to combine exposure from the various routes the aggregate risk index (ARI) approach was used to estimate risk. ARIs ≥ 1 are not of concern.

Acute Toxicity

The acute toxicity profile table for metofluthrin is below in Table 3.0.

Table 3.0 Acute Toxicity Profile – Metofluthrin Technical

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	46406719	LD_{50} >2000 mg/kg	III
870.1200	Acute dermal [rat]	46406721	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation [rat]	46406723	LC_{50} >1.08 mg/L and <1.96 mg/L	III
870.2400	Acute eye irritation [rabbit]	46406724	Not an eye irritant	IV
870.2500	Acute dermal irritation [rabbit]	46406724	Mildly irritating (PDI = 0.8)	IV
870.2600	Skin sensitization [Guinea pig]	46406726	Not a sensitizer	-

Toxicological PODs Used for Risk Assessment

The endpoint table used for the metofluthrin assessment is below in Table 3.1

Table 3.1: Summary of Toxicological Endpoints and Doses for Metofluthrin Occupational and Residential Risk Assessments.				
Exposure/ Scenario	Point of Departure	Uncertainty/ Safety Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Short-Term (1-30 days)	NOAEL= 15 mg/kg/day	UF_A= 10x UF_H= 10x UF_{DB} = 3x, <6 years of age	Residential LOC for children <6 years of age: **MOE = 300**	Developmental toxicity in the rat (oral, gavage) Maternal LOAEL = 30 mg/kg/day based on increased incidence of tremors in maternal animals.
Dermal Short-and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL= 300 mg/kg/day	UF_A= 10X UF_H=10X UF_{DB} = 3X, <6 years of age UF_{DB}= 1X, ≥6 years of age	Residential LOC for For children <6 years of age: **MOE = 300;** For individuals >6 years of age: **MOE = 100;** Occupational LOC **MOE = 100**	90-day dermal toxicity in the rat Systemic LOAEL = 1000 mg/kg/day based on mortality and clinical signs of toxicity including tremors and salivation.
Inhalation Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL = 0.099 mg/L Residential HEC = 0.052 mg/L **HED = 7.5 mg/kg/day** Occupational HEC = 0.155 mg/L **HED = 7.4 mg/kg/day**	UF_A= 3X UF_H=10X UF_{DB} = 3X, <6 years of age UF_{DB}= 1X, ≥6 years of age	Residential LOC for For children <6 years of age: **MOE = 100;** For individuals >6 years of age: **MOE = 30;** Occupational LOC: **MOE = 30**	28-day inhalation in the rat LOAEL = 0.196 mg/L based on mortality and clinical signs including tremors, hypersensitivity, abnormal gait, clonic convulsion and hypothermia. HEC = 0.103 mg/L HED = 14.8 mg/kg/day
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans at doses that do not result in a mitogenic response, based on negative genotoxicity data and mechanistic data supporting a non-linear mode of action (induction of cytochrome p450 with proliferative response) for liver tumors in male and female rats. Doses selected for risk assessment are protective of carcinogenicity.			

Absorption

Since the short- and intermediate-term dermal and inhalation PODs were based on route-specific toxicity studies, no absorption factors were necessary to estimate exposure.

Body Weight

The standard body weight for the general population (80 kg) for adults and 11 kg for children (1<2 years) was used for all exposure scenarios covered in this risk assessment since the endpoints selected were not developmental and/or fetal effects.

4.0 Use Profile

Table 4.0 (below) summarizes the proposed use pattern submitted on the product label by the registrant. The product is packaged in a 6.7 ounce container and consists of 0.23% active ingredient. It can be pre-set for 1, 2, or 3 hours of protection by the consumer; the battery operated device sprays at set intervals depending on the consumer settings.

Table 4.0. Summary of Directions for Use of Metofluthrin.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Use Directions and Limitations
Outdoor Residential Space			
Product can be set for 1, 2 or 3 hour intervals; spray interval is 40ms of spray every 33 seconds regardless of selected interval	4822-LIL-SGOL	437 mg active ingredient per 6.7 ounce can. Product designed to last for 30 hours of area repellent	Product automatically shuts off after selected use duration (e.g., shutdown after 1, 2, or 3 hrs)

The proposed product label prohibits use of the product indoors, or in tents, enclosed areas, or near food or food preparation areas.

5.0 Residential Exposure and Risk Estimates

The proposed use for metofluthrin is intended for consumers – i.e., it is considered a residential use for purposes of this exposure assessment. HED conducted an occupational and residential exposure assessment to support a proposed bed bug use of metofluthrin in September, 2012 (D397725). In that Section 3 assessment, the existing residential uses of metofluthrin were reassessed using the 2012 Residential SOPs and an up-to-date hazard database. There are currently no registered food uses for metofluthrin and drinking water exposure is not expected from the registered or the proposed bed bug control uses of metofluthrin; therefore, an aggregate risk assessment is not needed.

5.1 Residential Handler Exposure/Risk Estimates

HED uses the term “handlers” to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

The metofluthrin-based product FAN does not require a residential handler assessment as handler exposure is expected to be negligible. The product is loaded with cartridges by the handler and the product is released by a timer mechanism without mixing, loading, or applying in the traditional sense. Adult and child post-application exposure (inhalation &dermal for adults and children, and incidental oral for children only) are expected as the primary exposure routes.

5.2 Residential Post-application Exposure/Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with metofluthrin. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Post-application inhalation exposure (adults/children) from use of the battery operated area repellent
- Post-application dermal exposure (adults/children) from contact surfaces where sprays have settled
- Post-application incidental oral exposure (children) from contact with areas where sprays have settled

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[3] and the hazard profile table in section 3.0 of this document. These lifestages are not the only lifestages that could be potentially exposed for these post-application scenarios; however, the assessment of these lifestages is health protective for the exposures and risk estimates for any other potentially exposed lifestages.

Residential Post-application Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[3].

Residential Post-application Non-Cancer Exposure and Risk Equations
The algorithms used to estimate residential post-application exposure and dose can be found in Appendix A and/or the 2012 Residential SOPs[3].

5.2.1 Post-application Inhalation Exposure and Risk Estimates

As identified above, post-application inhalation exposure is a likely exposure scenario for the metofluthrin-based FAN product for adults and children. This assessment follows the post-application inhalation exposure for outdoor aerosol sprays outlined in the 2012 Residential SOPs with the following modifications:

- The 43.7 mg ai/day exposure estimate is based on the use of the product for 3 hours.
- The product label indicates that label claims will be made for a 12' x 12' treatment area **and** a 225 ft^2 treatment area. The discrepancy is a result of the results of the efficacy testing versus most simply explaining the treatment area on consumer packaging. The standard assumptions for treated area have been modified from the defaults to match the relevant treatment area. See Appendix A for more detail.

[3] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

Table 5.2.1 - Post-application Inhalation Exposure and Risk Estimates for Metofluthrin						
Lifestage	Application rate (mg ai/day)	Inhalation Rate (m^3/hr)	Q* (m^3/hr)	Exposure (mg/day)	Absorbed Dose (mg/kg/day)	Inhalation MOE (rounded)
Adults	43.68735	0.64	3204	0.01	0.000109	69,000
Children (1 <2 years)	43.68735	0.33	3204	0.00	0.000409	18,000

- Q = airflow through the treated space.
- Appendix A details the exposure calculations and the departure from defaults for the Q and A_{cross} inputs.

5.2.2 Post-application Dermal Exposure and Risk Estimates

As identified above, post-application dermal exposure is a likely exposure scenario for the metofluthrin-based FAN product for adults and children. This assessment follows the post-application inhalation exposure for outdoor aerosol sprays outlined in the 2012 Residential SOPs with the following modifications:

- The calculated deposition of 6.7E-07 lb ai/ft^2 deposition represents a 3 hour use of the product settled onto turf surrounding the treated area.
- See the explanation above in Section 5.2.1. regarding the product treatment area. The proposed product label indicates claims will be made for a 12' x 12' treatment area **and** a 225 ft^2 treatment area, depending on specific product labels. The claims will not be mixed on the end-use consumer labels. The area treated has been modified from the defaults to match the relevant treatment area (affecting the deposited residue calculation). See Appendix A for more detail.

Table 5.2.2 - Post-application Dermal Exposure and Risk Estimates for Metofluthrin							
Lifestage	Deposited Residue (lb ai/ft^2)	Fraction transferred	Transfer Coefficient (cm^2/hr)	Exposure Time (hr/day)	Exposure (mg/day)	Absorbed Dose (mg/kg/day)	Dermal MOE (rounded)
Adults	4.28056E-07	0.01	180,000	1.5	0.9	0.01	27,000
Children (1 <2 years)	4.28056E-07	0.01	49,000	1.5	0.2	0.02	14,000

- Appendix A details the exposure calculations

The risk estimates calculated above in Table 5.2.2 involve conservative exposure calculations – specifically, that the treatment area is a 12' x 12' area. The above calculations involve post-application dermal exposure to a 12' x 12' treated area. The label claims for 225 ft^2 treatment area would have correspondingly lower exposures (i.e., higher calculated MOEs). Either way the

dermal (or incidental oral) exposure is calculated, the risk estimates are significantly higher than the respective LOCs for adults or children.

5.2.3 Post-application Incidental Oral Exposure and Risk Estimates

As identified above, post-application incidental exposure is a likely exposure scenario for the metofluthrin-based FAN product for children. This assessment follows the post-application inhalation exposure for outdoor aerosol sprays outlined in the 2012 Residential SOPs with the following modifications:

- The calculated deposition of 6.7E-07 lb ai/ft^2 deposition represents a 3 hour use of the product settled onto turf surrounding the treated area.
- See the explanation above in Section 5.2.1. regarding the product treatment area. The proposed product label indicates claims will be made for a 12' x 12' treatment area **and** a 225 ft^2 treatment area, depending on specific product labels. The claims will not be mixed on the end-use consumer labels. The area treated has been modified from the defaults to match the relevant treatment area (affecting the deposited residue calculation). See Appendix A for more detail.
- The rest of the exposure factors identified in Appendix A represent the default values to assess incidental oral (i.e., hand-to-mouth) exposure of children (the lifestage assessed represents children 1 < 2 years of age).

Table 5.2.2 - Post-application Incidental Oral Exposure and Risk Estimates for Metofluthrin

Lifestage	Absorbed Dose (mg/kg/day)	MOE (rounded)
Children (1 <2 years)	0.0004	33,000

- Appendix A details the exposure calculations

5.3 Combined Residential Exposure and Risk Estimates

Since dermal and incidental oral exposure routes share a common toxicological endpoint, risk estimates have been combined for those routes. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related and it is likely that they occur interspersed amongst each other across time. Combining these scenarios with the dermal exposure scenario would be overly-conservative because of the conservative nature of each individual assessment. Therefore, the post-application exposure scenarios that were combined for children 1 < 2 years old are the dermal, inhalation, and hand-to-mouth scenarios. This combination should be considered a protective estimate of children's exposure to pesticides used around the home.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

Table 5.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Metofluthrin.

Lifestage	Post-application Exposure Scenario		Application Rate[1]	Dose (mg/kg/day)[2]	MOEs[3]	Combined Routes (X indicates included in Combined MOE)	ARI[4]
	Use Site	Route of Exposure					
Adult		Inhalation	3 hours of product use; 43.7 mg ai	0.000109082	69,000	X	240
		Dermal		0.01103	27,000	X	
Child		Inhalation	3 hours of product use; 43.7 mg ai	0.0004	18,000	X	27
		Dermal		0.022	14,000	X	
		Incidental Oral		0.0004	33,000	X	

1 Assessment is based on exposure to 3 hours of daily product use on proposed label (Reg. No. 4822-LIL-SGOL) for the duration of the short-term exposure duration.

2 Dose (mg/kg/day) equations: See Appendix A for the dose calculation equations for the inhalation, dermal, and incidental oral routes of exposure.

3 MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day). where Short-term Dermal PoD = NOAEL of 300 mg/kg/day and level of concern = 100 for adults and 300 for children < 6 years old).

4 Adult/Child Aggregate Risk Index =

Adult = $1/ [(1/ARI_{Dermal}) + (1/ARI_{inhalation})]$.

Child = $1/ [(1/ARI_{Dermal}) + (1/ARI_{Inhalation}) + (1/ARI_{Hand\text{-}to\text{-}Mouth})]$.

5.3 Combined Residential Risk Estimates (Multiple Exposure Scenarios)

Metofluthrin does have multiple products with current registrations. However, HED does not believe that the proposed use pattern assessed in this document is likely to co-occur with the other registered metofluthrin use patterns (bed bug use, area mosquito repellent). The September 2012 human health risk assessment (D402777, D403390) contains additional information.

5.4 Residential Risk Estimates for Use in Aggregate Assessment

No aggregate assessment is required for metofluthrin as there are currently no registered food uses for metofluthrin and exposure to residues in drinking water is not expected from the registered or the proposed area repellent uses of metofluthrin; therefore, an aggregate risk assessment is not needed.

However, the residential exposure use pattern assessed in this document for metofluthrin as an area mosquito repellent did not identify risks of concern (ARI's for adults and children are 240 and 27, respectively).

5.6 Residential Bystander Post-Application Inhalation Exposure

In the case of metofluthrin, a residential post-application inhalation exposure assessment was performed. This exposure scenario is representative of a worse case inhalation exposure and should be considered protective of other individuals in the vicinity of the area repellent product.

6.0 Cumulative Exposure/Risk Characterization

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has determined that the pyrethroids and pyrethrins, including metofluthrin, share a common mechanism of toxicity (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment for the pyrethroids/pyrethrins was published on Nov. 9, 2011 (USEPA, 2011a) and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. Further information about the determination that pyrethroids and pyrethrins share a common mechanism of toxicity may be found in document ID: EPA-HQ- OPP-2008-0489-0006.

While metofluthrin has been included as an active ingredient in the pyrethroid cumulative assessment, the exposure scenarios covered in this assessment (i.e., outdoor repellent uses) were not exposure scenarios addressed in the 2011 pyrethroid cumulative risk assessment. For that effort, the Agency focused on the four main (i.e., high potential exposure) pyrethroid residential use scenarios – turf, pets, gardens, and indoors (e.g., fogger and crack and crevice applications). Based on a qualitative review of the proposed use pattern and resulting risk estimates for metofluthrin, the Agency has c determined that it will not change the overall findings presented in the pyrethroid cumulative risk assessment. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

7.0 Occupational Exposure and Risk Estimates

7.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is not expected from the proposed uses. A recent (September, 2012) HED risk assessment (D402777, D403390) assessed both the existing and proposed new uses of metofluthrin to support registration review. The

accompanying ORE chapter further the details the quantitative assessment of metofluthrin for occupational and residential exposure. Besides the proposed action, there are no additional new uses of metofluthrin-based products. HED did not identify any occupational exposure concerns in the September 2012 risk assessment. In that assessment, all commercial handler scenarios resulted in ARIs greater than the LOC (i.e. ARI>1) with baseline attire (i.e., single layer of clothing, no respirator).

7.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). HED did not conduct a quantitative post-application exposure assessment in the September 2012 risk assessment for metofluthrin because the presence of commercial handlers in treated residential or commercial areas is minimal after application, due to the lack of post-application activities involved in treating structures. Therefore, a quantitative post-application exposure and risk assessment was not required for commercial handlers.

Appendix A. Summary of Occupational and Residential Non-cancer Algorithms

Residential Non-cancer Handler Algorithms

Not applicable for metofluthrin

Residential Non-cancer Post-application Algorithms

The following algorithm is used to determine post-application inhalation exposure to outdoor aerosol space sprays:

$$E = \frac{IR * AR}{Q}$$

where:

E	= exposure (mg/day);
IR	= inhalation rate (m^3/hour);
AR	= application rate (mg ai/day); and
Q	= airflow through the treated area (m^3/hour).

The airflow through the treated space can be calculated as follows:

$$Q = AV * CF1 * CF2 * A_{cross\text{-}section}$$

where:

Q	= airflow through treated space (m^3/hr);
AV	= air velocity (m/s);
CF1	= time unit conversion factor (60 seconds/1 minute);
CF2	= time unit conversion factor (60 minutes / hour); and
$A_{cross\text{-}section}$	= cross-section of outdoor space treated (m^2).

Application rate can be calculated as follows:

$$AR = A_{product} * A.I. * CF1 * N$$

where:

AR	= application rate (mg ai/ day);
$A_{product}$	= amount of product in 1 can (oz or g/can);
A.I.	= percent active ingredient in product (% ai);
CF1	= weight conversion factor (28,350 mg/oz or 1,000 mg/g); and
N	= number of cans applied per day in one application (cans/day).

Alternatively, if the aerosol can contents are expressed as a volume in milliliters, the application rate for use in the exposure assessment can be calculated as follows:

$$AR = A.I. * A_{product} * CF * D_{product} * N$$

where:

AR = application rate (mg ai/day);
A.I. = percent active ingredient in product (% ai);
$A_{product}$ = amount of product per can (mL/can);
CF = conversion factor to convert grams to milligrams (1,000 mg/1 g);
$D_{product}$ = density of product (g/mL); and
N = number of cans applied per day in one application (cans/day).

Absorbed inhalation dose normalized to body weight is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

D = dose (mg/kg-day);
E = exposure (mg/day);
AF = absorption factor (inhalation); and
BW = body weight (kg).

Table A-1: Outdoor Aerosol Space Sprays –Inputs for Residential Post-application Inhalation Exposure

Algorithm Notation	Exposure Factor (units)		Point Estimate(s)
AR	Application rate (mg ai/ day)		**43.7 (based on use pattern)**
$A_{cross\text{-}section}$	Cross sectional area of area treated (m^2)		8.9
AV	Air velocity (m/s)		0.1
Q	Airflow through treated area (m^3/hr)		3,204
N	Number of cans applied per day in one application (cans/day)		1
$D_{product}$	Density of product (g/mL)	Product specific density	0.63 (product specific)
A.I.	Percent ai in product (%)		**0.23**
$A_{product}$	Amount of product (oz/can)		**6.7**
IR	Inhalation rate (m^3/hour)	Adult	0.64
		Children (1 < 2 years old)	0.33
BW	Body Weight (kg)	Adult	80
		Children (1 < 2 years old)	11

Post-application Dermal Exposure Algorithm

The following equation can be used to convert the application rate in pounds ai per square foot as is deposited on the turf:

$$AR = \frac{A_{product} * A.I. * CF1 * N}{T_A}$$

where:

AR = application rate (lb ai/ft^2 or lb ai/A);
$A_{product}$ = amount of product per can (oz or g/can);
A.I. = percent active ingredient in product (% ai);
CF1 = weight conversion factor (1 lb/16 oz or 1 lb/454 g);
N = number of cans applied per day in one application (cans); and
T_A = treated area (ft^2 or A).

Alternatively, if the aerosol can contents are expressed as a volume in milliliters, the application rate for use in the exposure assessment can be calculated as follows:

$$AR = \frac{A_{product} * A.I. * CF * D_{product} * N}{T_A}$$

where:

AR = application rate (lb ai/ft^2 or lb ai/A);
A.I. = percent active ingredient in product (% ai);
$A_{product}$ = amount of product per can (mL/can);
CF = conversion factor (1 lb/454 g);
$D_{product}$ = density of product (g/mL);
N = number of cans per day in one application (cans); and
T_A = treated area (ft^2 or A).

The algorithm to calculate exposure is as follows:

$$E = TTRt * CF1 * TC * ET$$

where:

E = exposure (mg/day);
TTR_t = turf transferable residue on day t (µg/cm2);
CF1 = weight unit conversion factor (0.001 mg/µg);
TC = transfer coefficient (cm2/hr); and
ET = exposure time (hr/day).

If chemical-specific TTR data are available, then surface residues from the day of application should be used (assume that individuals could be exposed to residues immediately after application). However, if data are not available, then TTR_t can be calculated using the following formula:

$$TTRt = AR * F * (1-F_D)t * CF2 * CF3$$

where:

TTR_t = turf transferable residue on day t ($\mu g/cm^2$);
AR = application rate (lbs ai/ft^2 or lb ai/acre);
F = fraction of ai as transferable residue following application (unitless);
F_D = fraction of residue that dissipates daily (unitless);
t = post-application day on which exposure is being assessed;
CF2 = weight unit conversion factor (4.54×10^8 μg/lb); and
CF3 = area unit conversion factor (1.08×10^{-3} ft^2/cm^2 or 2.47×10^{-8} acre/cm^2).

Table A-3: Outdoor Aerosol Space Sprays -- Inputs for Residential Post-application Dermal Exposure			
Algorithm Notation	**Exposure Factor (units)**		**Point Estimate(s)**
A.I.	Percent ai in product (%)		**0.23**
$A_{product}$	Amount of product (oz/can)		**6.7**
N	Number of cans applied per day in one application (cans/day)		1
$D_{product}$	Density of product (g/mL)	Water-based products	0.63 (product specific)
		Solvent-based products	
T_A	Treated area (ft^2 or A)		12 ft. x 12 ft. [x 8 ft] 144 ft^2 (although the product label can alternately claim 225 ft^2) based on efficacy testing
AR	Application rate (mass active ingredient per unit area)		$6.68E^{-07}$ lb ai/ft^2 (calculated based on treatment area of 144ft^2)
F	Fraction of AR as TTR following application (if chemical-specific data is unavailable)		0.01
F_D	Daily residue dissipation (if chemical-specific data is unavailable) (fraction)		0.1
TC	Transfer Coefficient (cm^2/hr)	Adults	180,000
		Children 1 < 2 years old	49,000
ET	Exposure Time (hours per day)	Adults	1.5
		Children 1 < 2 years old	1.5
BW	Body Weight (kg)	Adults	80
		Children 1 < 2 years old	11

Post-application Hand-to-Mouth Exposure Algorithm

Exposure from hand-to-mouth activity is calculated as follows (based on the algorithm utilized in the SHEDS-Multimedia model):

$$E = [HR * (F_M * SA_H) * (ET * N\_Replen) * (1- (1- SE)^{(Freq\_HtM/N-Replen)})]$$

where:

E = exposure (mg/day);
HR = hand residue loading (mg/cm^2);
FM = fraction hand surface area mouthed / event (fraction/event);
SAH = typical surface area of one hand (cm^2);
ET = exposure time (hr/day);
N_Replen = number of replenishment intervals per hour (intervals/hour);
SE = saliva extraction factor (i.e., mouthing removal efficiency); and
Freq_HtM = number of hand-to-mouth contacts events per hour (events/hour).

and

$$HR = \frac{Fai_{hands} * DE}{SA_H * 2}$$

where:

HR = hand residue loading (mg/cm^2);
Fai_{hands} = fraction ai on hands compared to total surface residue from dermal transfer coefficient study (unitless);
DE = dermal exposure (mg); and
SA_H = typical surface area of one hand (cm^2).

Dose, normalized to body weight, is calculated as:

$$D = \frac{E}{BW}$$

where:

D	= dose (mg/kg-day);
E	= exposure (mg/day); and
BW	= body weight (kg).

Table A-4: Outdoor Aerosol Space Sprays – Inputs for Residential Post-application Hand-to-Mouth Exposure

Algorithm Notation	Exposure Factor (units)	Point Estimate(s)
Fai_{hands}	Fraction of ai on hands from dermal transfer coefficient study (unitless)	0.06
DE	Dermal exposure (mg)	Calculated = 0.2
SA_H	Typical surface area of one hand (cm^2), children 1 < 2 years old	150
AR	Application rate (mass active ingredient per unit area)	6.68E^{-07} lb ai/ft^2

Table A-4: Outdoor Aerosol Space Sprays – Inputs for Residential Post-application Hand-to-Mouth Exposure			
Algorithm Notation	**Exposure Factor (units)**		**Point Estimate(s)**
			(calculated based on treatment area of $144ft^2$)
HR	Residue available on the hands (mg/cm^2)		Calculated via (DE * Fai_{hands})/SA_H
F_M	Fraction hand surface area mouthed (fraction/event)		0.13
N_Replen	Replenishment intervals per hour (intervals/hr)		4
ET	Exposure time (hrs/day)		1.5
SE	Saliva extraction factor (unitless)		0.48
Freq_HtM	Hand-to-mouth events per hour (events/hr)		13.9
BW	Body Weight (kg)	Children 1 < 2 years old	11

Appendix B. Metofluthrin - Calculations of RDDR, HEC and HED

Calculations were based on the US EPA "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry," October, 1994. Publication EPA/600/8-90/066F.

Study used: MRID 46406736, 28-week inhalation toxicity study in the rat

Exposure concentrations (aerosol) tested in the rat: 0, 0.01, 0.051, 0.099 or 0.196 mg/L. Animals exposed for 4 hours per day, 7 days per week for 28 consecutive days.

1. RDDR (Regional Deposited Dose Ratio of particles for respiratory tract region): **3.14** calculated using the RfC (Reference Concentration) methodology computer program using the following inputs and the program's default human inputs:

   NOAEL (No Observed Adverse Effect Level): 0.099 mg/L
   MMAD (mass median aerodynamic diameter): 2.47 µm
   GSD (geometric standard deviation: 2.02
   Animal body weight: 185 g (rounded-up initial bw for males)

   $$RDDR = \frac{RDD_r/\text{Normalizing Factor})_A}{RDD_r/\text{Normalizing Factor})_H}$$

   Where RDD is the regional deposited dose of particles and r represents the extrathoracic, tracheobronchial and pulmonary respiratory tract regions

2. HEC (Human Equivalent Concentration, expressed as mg/L): NOAEL in mg/L x RDDR x [hours/day exposure, animals ÷ hours/day exposure, humans] x [exposure days/week, animals ÷exposure days/week, humans]

   Occupational HEC:

   0.099 mg/L x 3.14 x [4 hours/day ÷ 8 hours/day] x [7 days ÷ 7 days]
   = 0.099 mg/L x 3.14 x 0.5 x 1
   = 0.155 mg/L

   Non-occupational HEC

   0.099 mg/L x 3.14 x [4 hours/day ÷ 24 hours/day] x [7 days ÷ 7 days]
   = 0.099 mg/L x 3.14 x 0.167 x 1
   = 0.052 mg/L

3. HED (Human Equivalent Dose, expressed as mg/kg/day): HEC (mg/L) x human conversion factor (6 L/hrs/kg) x duration of daily exposure (hrs)

   Occupational HED:

   0.155 mg/L x 6 L/hrs/kg x 8 hrs
   = 7.4 mg/kg/day

   Non-occupational HED:

   0.052 mg/L x 6 L/hrs/kg x 24 hrs
   = 7.5 mg/kg/day