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Alexander B. Grannis
Commissioner

June 16, 2008

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ms. Jody L. Thrune
S.C. Johnson & Son, Inc.
1525 Howe Street
Racine, Wisconsin 53403

Dear Ms. Thrune:

Re: Registration of OFF! Insect Repellent Fan (EPA Reg. No. 4822-542) and OFF! Insect Repellent Fan Refill (EPA Reg. No. 4822-542) which contain the New Active Ingredient Metofluthrin (Chemical Code 109709) (Company Number 4822)

The New York State Department of Environmental Conservation (Department) has reviewed your application, received June 25, 2007, to register **OFF! Insect Repellent Fan** (EPA Reg. No. 4822-542) and **OFF! Insect Repellent Fan Refill** (EPA Reg. No. 4822-542). These products contain the new active ingredient **metofluthrin** (Chemical Code 109709).

The OFF! Repellent Fan is a device that is worn on the belt of humans or placed on a flat surface, and consists of a fan and a disc containing the active ingredient metofluthrin in a liquid form. The fan is run by two AA batteries, and passes air over the disc, thus creating an "area of personal protection from mosquitos." The label recommends that the disc be replaced every three weeks.

The application was deemed complete for purposes of review on August 20, 2007, and a registration decision was due by January 17, 2008. The Department indicated in the completeness letter that very limited efficacy data had been provided in the application package and requested that all information held by S.C. Johnson on this subject be submitted to help in evaluating any potential benefits of this product. Additional information was received on September 10, 2007. After evaluating this information, the Department discussed their concerns with S.C. Johnson and, as a result, the registration date was waived by S.C. Johnson. On January 15, 2008, the Department sent a letter outlining their concerns with the application and information was received in response to that letter on January 28, 2008.

The registration of these products is based on the technical review by the New York State Department of Health (DOH) for impacts to human health based on all information received from S.C. Johnson.

During the initial technical review of the application, the Department determined that the active ingredient metofluthrin was not very acutely toxic to laboratory animals by the oral, dermal or inhalation routes of exposure. It was not an eye irritant (tested on rabbits) nor a skin sensitizer (tested on guinea pigs), but did cause some mild eye irritation (tested on rabbits). Acute toxicity testing on the formulated end product was waived, as it is a repellent device with the active ingredient impregnated on removable disks.

Metofluthrin caused toxic effects in subchronic animal feeding studies. In a 90-day rat feeding study, liver toxicity (increased liver weights, histopathology and clinical chemistry changes) in both sexes and decreased body weight gain in females was observed at doses of 71 and 73 milligrams per kilogram body weight per day (mg/kg/day), in male and female animals, respectively. The respective no-observed-effect levels (NOELs) were 21 and 22 mg/kg/day. Similar liver toxicity was also noted in a 90-day feeding study in mice at doses of 48.7 and 58.7 mg/kg/day for males and females, respectively. The respective NOELs for males and females were 35.7 and 43.9 mg/kg/day. Metofluthrin also caused tremor and vomiting in dogs in a 90-day feeding study at 100 mg/kg/day; the NOEL was 30 mg/kg/day. Hyperactivity and vocalization in the females during the daily exposure period was observed in a 90-day dermal toxicity study in rats at 30 mg/kg/day; a NOEL was not established for this study. Finally, metofluthrin caused mortality and clinical signs (including tremors, hypersensitivity, ataxic gait, tiptoe gait, lateral position, clonic convulsion, and hypothermia in both sexes) in a 28-day inhalation study at air concentrations of 196 milligrams per cubic meter of air (mg/m3); the NOEL was 99 mg/m3.

Metofluthrin also caused some toxic effects in chronic animal feeding studies. In a one-year dog feeding study, an increased incidence of tremor was observed in males at 30 mg/kg/day; the NOEL was 10 mg/kg/day. In a chronic feeding study in rats, liver toxicity (histopathology) and decreased body weights and body weight gains in both sexes, as well as kidney lesions in males were observed. In males, the above-noted toxic effects occurred at a dose of 38.1 mg/kg/day, whereas in females, the effects occurred at 47.4 mg/kg/day. The respective NOELs for males and females were 8.2 and 10.1 mg/kg/day. In a chronic feeding study in mice, metofluthrin caused decreased body weight gain at 209 mg/kg/day and 277 mg/kg/day, for males and females respectively. The respective NOELs were 116 mg/kg/day and 155 mg/kg/day.

In developmental toxicity studies on pregnant rats and rabbits, no developmental effects were observed in offspring of either species up to the highest doses of metofluthrin tested, which were 30 mg/kg/day (rat) and 250 mg/kg/day (rabbits). Maternal effects were observed in rats (increased incidence of tremor) at 30 mg/kg/day, with a NOEL of 15 mg/kg/day, and in rabbits (increased mortality) at 125 mg/kg/day, with a NOEL of 25 mg/kg/day. In a rat multigeneration reproductive study, no effects on reproductive parameters were noted at doses up to 310.4 mg/kg/day in males and 339.7 mg/kg/day in females (the highest doses tested).

Metofluthrin caused effects in acute and subchronic neurotoxicity studies in rats. In the acute neurotoxicity study, tremors, twitches, abnormal respiration, increased motor activity, and mortality were observed after a single metofluthrin dose of 100 mg/kg; the NOEL was 50 mg/kg. In the subchronic neurotoxicity study, this chemical caused tremors and twitches in females at 206 mg/kg/day; the NOEL was 68.8 mg/kg/day. No clinical signs of neurotoxicity were noted in males at doses up to 178.8 mg/kg/day, the highest dose tested. Neither study reported evidence of

neurohistopathology.

The United States Environmental Protection Agency (USEPA) classified metofluthrin as "likely to be carcinogenic to humans." This was largely based on the fact that male and female rats fed this chemical showed a statistically significant increased incidence of hepatocellular adenomas, carcinomas, and combined adenomas/carcinomas at doses greater than or equal to 38.1 mg/kg/day. There were no treatment related tumor increases in male or female mice. Metofluthrin was also negative in a number of genotoxicity studies. As stated by the USEPA, "Metofluthrin does not operate via a cytotoxic or mutagenic MOA (mode of action), nor does it cause peroxisome proliferation." The USEPA derived a cancer potency factor (CPF) of 1.62 x 10 -2 (mg/kg/day) -1, based on the increased incidence of liver tumors in female rats."

The USEPA conducted a noncancer risk assessment for incidental oral, dermal, and inhalation exposures to metofluthrin from the use of the OFF! Repellent Fan pesticide product by consumers. Due to the seasonal nature of most insect repellent use, only short-term exposure scenarios were considered. Margins of exposure (MOEs) were estimated as follows: (a) incidental oral exposures to children only were compared to a NOEL of 15 mg/kg/day from a rat developmental toxicity study; (b) dermal exposures to adults and children were compared to a NOEL of 300 mg/kg/day from a 90-day rat dermal toxicity study; and (c) inhalation exposures to adults and children were compared to a NOEL of 16 mg/kg/day from a 28-day rat inhalation toxicity study. Estimated MOEs for each of the exposure scenarios ranged from 15,000 to 940,000 for children and from 44,000 to 1,900,000 for adults. Generally, the USEPA considers MOEs of 100-fold or greater to provide adequate protection.

The USEPA also estimated the inhalation and dermal cancer risk, using the CPF of 1.62×10^{-2} $(mg/kg/day)^{-1}$, from the consumer use of this pesticide product. The Agency assumed that the OFF! Repellent Fan would be used 12 hours per day, 12 times per year (based on estimated usage of insect repellents containing DEET) for 50 years of a 70-year life span. The estimated upper bound cancer risk was 1.5×10^{-5} assuming a saturated air concentration of metofluthrin of 0.28 mg/m^3 based on the Ideal Gas Law. The Agency also utilized exposure data from a registrant supplied mannequin study to estimate cancer risk. Air samples were taken at various locations on and around a child and an adult mannequin when the adult mannequin was equipped with the fan device. Metofluthrin was not quantifiable in any of the air samples taken, so the level of quantification (0.00012 mg/m3) was used as an air concentration to estimate exposure. Using this approach, the cancer risk from inhalation exposure was estimated to be 6.5×10^{-9}. To estimate cancer risks from dermal exposures, the Agency used potential daily dermal exposure estimated from the mannequin study, similar product use assumptions as above and a dermal absorption of 17%. The cancer risk from dermal exposure was estimated to be 4.6×10^{-7}.

The registrant submitted summaries of two efficacy studies that evaluated the fan product against mosquitoes when worn by humans. These studies were conducted in the field in Michigan and Florida, with several mosquito species present in each location. In the Michigan study, the device was evaluated in the first hour of operation and again after the product had been operating for 11 hours. Percent landing reductions over control subjects ranged from 84% to 100%, with most points of evaluation demonstrating 100% reduction. In the Florida study, percent landing reduction ranged from 59% to 100% when evaluated in the first, sixth and twelfth

hours of operation, with most points of evaluation demonstrating reductions in the 90% to 100% range. It was not stated whether the devices used in the studies were units that had remained only partially used for a period of time (e.g., days or weeks to simulate storage) prior to evaluation, or if they were new on the day of testing. No testing data were provided for insects other than mosquitoes.

Based on the information submitted initially with the application, the Department had concerns for registering a personal repellent device that disperses a likely human carcinogen into the immediate surroundings of the user and those near them. Several specific concerns were identified as follows:

- The basic application mode of this product actively disperses a pyrethroid insecticide into the air space around the user, which does not seem to be a discrete approach to personal protection from mosquitoes.
- The active ingredient has carcinogenic potential.
- The product lends itself to misuse (e.g., individuals using the fan as a personal cooling device) and use where exposure could be increased (e.g., in confined spaces, either intentionally or if one forgets to turn the device off, using more than one device per person).
- The product represents an attractive object for children who may play with the device or gain access to and dermally contact or mouth the active ingredient in the refill (the device is not in child-resistant packaging).
- The product contains misleading packaging statements including use of the terms “repellent” and “insect repellent” in the product name, which may lead users to believe that it will repel insects of many types (efficacy data were only provided for mosquitoes), as is the case with most other registered insect repellents.

The Department conveyed these concerns to S.C. Johnson in a letter dated January 15, 2008. The registrant responded to each of these issues with additional information or comments.

Regarding the application mode of the repellent fan product, the registrant states that the closest comparable products are mosquito candles, coils, lanterns and sticks containing citronella or pyrethrins/pyrethroids. Many of these products are registered in the State. They indicated that these alternate products are not as effective as the mosquito fan, and require heat or combustion to disperse the material, which poses its own set of concerns.

To address the concern for the carcinogenicity of metofluthrin, the registrant submitted the Second Report of the Cancer Assessment Review Committee (CARC), July 26, 2007. This report contains a reanalysis of metofluthrin’s carcinogenicity that includes data not available during the committee’s first review on April 19, 2006 (this first assessment was the only report submitted during the Department’s initial review of the fan product). The committee determined that the new data were sufficient to support a mitogenic mode of action for the development of liver tumors in rats exposed to metofluthrin in the carcinogenicity study. The report summarized mode of action study data that characterized effects such as increased P450 enzyme levels, increased smooth endoplasmic reticulum, hepatocellular hypertrophy, hepatocellular proliferation and inhibition of intracellular communication, which were described as steps leading to tumor development via a nongenotoxic mechanism (i.e., mitogenicity). Some of these studies used sodium phenobarbital as a positive control because this compound induces tumors in rodents via a

mitogenic mode of action. The additional data on mode of action reviewed by the CARC in their second analysis addressed their previous uncertainties, and the committee revised their classification for metofluthrin to "not likely to be carcinogenic to humans at doses that do not induce a mitogenic response." The CARC further indicated that quantification of cancer risk is not required.

The registrant did not agree with the Department's concern that the product lends itself to misuse. The registrant contends that the fan product is less likely than alternate registered products, such as candles and coils, to be misused indoors. They also indicate that due to the high cost of the fan, people are not likely to use more than one unit at a time. And, they contend that people are more likely to apply too much topical repellent or to burn too many candles and coils, each of which pose greater risks. Moreover, they state that the fan would not be misused as a personal cooling device because "…the strength of the airflow from the unit is barely perceptible,…." The product label also has the precautionary statement "Do not use indoors or in enclosed spaces."

The registrant also submitted information to address the concern that children would be attracted to this product. One risk analysis was conducted for this product based on what is known about the behavior of children (and older individuals) and the hazards inherent in the fan product. This analysis concluded that the product poses a low overall risk for people of any age. The registrant also provided a letter from a psychologist who discussed the attributes of an object that make it attractive to children. This psychologist concluded that the fan product does not possess characteristics that would make it attractive to children to interact with or to play with as a toy. The registrant also submitted verification from USEPA that the product, given its acute toxicity profile, does not require child-resistant packaging. Finally, the registrant has made changes that address our concerns about product labeling. Specifically, the product is now clearly labeled as a "mosquito repellent," not the broader, previous claim of being an "insect repellent" that might lead consumers to think the product will protect them from ticks, black flies, etc. The registrant also made other label claims that serve to make the use instructions more clear to consumers.

The registrant responded to the concerns expressed in our initial review letter as discussed above. The registrant indicated that there are numerous other products that can be used to repel mosquitoes which would also result in inhalation or dermal exposures, and in some cases, pose a skin burn or fire hazard. The registrant noted the evidence that metofluthrin has a nongenotoxic mode of action and that USEPA revised their classification of methofluthrin to "not likely to be carcinogenic to humans at doses that do not induce a mitogenic response." Further, the USEPA indicated that they have sufficient evidence to recommend moving away from using a low-dose extrapolation approach for estimating cancer risks (nevertheless, risks quantified using this approach, as indicated in our initial review letter, are within the range that is generally considered to be acceptable). Also, the use of this product is likely to be sporadic and for only a portion of the year, decreasing the likelihood of developing chronic effects. The registrant also presented some discussion about the potential for misuse of this product, which concludes that this potential is low. This conclusion, however, may have a subjective basis.

Overall, the risks posed by the OFF! Repellent Fan and OFF! Repellent Fan Refills products appear to be low, and the registrant has generally addressed our concerns, including

making some label changes for clarification. However, the Department continues to have some uncertainty regarding the potential for misuse of these products. Therefore, as a condition of registration, the registrant is required to provide us with a summary of any adverse effects that have been associated with these products, including any FIFRA 6(a)(2) reports, on a quarterly basis.

Enclosed are your Certificate of Pesticide Registration and New York State stamped "ACCEPTED" labels.

S.C. Johnson is reminded that if New York State registration is requested for either of these products, or any other metofluthrin product, which contain an expansion of use patterns or potentially increase exposure, the product will be considered a **Major Change in Labeling and the Department will require an extensive review.**

If you have any questions, please contact Samuel Jackling, Chief of our Pesticide Product Registration Section, at (518) 402-8768.

Sincerely,

Maureen P. Serafini

Maureen P. Serafini
Director
Bureau of Pesticides Management

Enclosures

ecc: w/enc. - R. Mungari, NYS Dept. A&M
A. Grey/E. Horn, NYSDOH
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