COMPARATIVE SAFETY OF RECENTLY REGISTERED NEW ACTIVE INGREDIENTS IN CALIFORNIA

#1037

C. N. Aldous and P. Leung

Medical Toxicology Branch, Department of Pesticide Regulation., Cal/EPA, Sacramento, CA 95814

INTRODUCTION

Contemporary regulatory and economic pressures might be expected to foster the development of pesticides which are safer to humans and non-target species than were previous generation pesticides. An evaluation of pesticides registered as "new active ingredients" by the California Department of Pesticide Regulation (DPR) during the time frame of 2007 through 2009 supports that supposition. This presentation first sorts these "new" active ingredients (AI's) into broad categories, which relate to the laboratory animal safety data required for registration. Out of a total of 48 "new" AI's, 18 were novel synthetic materials for which a standard set of FIFRA-mandated laboratory animal studies was required. Six AI's were sufficiently similar to existing registered compounds that chronic, oncogenicity, reproductive, and developmental toxicity (CORT) data from analogous previously-registered compounds were considered sufficient for assessment. Six other "new" AI's were actually materials for which lapsed registrations were being renewed, typically presented with a legacy of CORT studies. CORT studies were not required for an additional 15 AI's which were either formally considered by U.S. EPA as "reduced risk" (RR) materials, or otherwise would unlikely be considered chemicals of concern. The final 3 "new" entries are synthetic materials for which most of the CORT studies were not required, due to comparatively limited exposures and a non-food use pattern.

As a general indicator of safety of the subset of 16 novel synthetic compounds, DPR reviews of the CORT studies were assessed to determine whether reviewers designated outcomes of any CORT studies to be "adverse" (flagging attention to prioritization for risk assessment). Seven of these compounds had no CORT studies with "adverse" outcomes, whereas 11 had one or more flagged CORT studies. In each of the latter 11 cases, major features of "adverse" effects are presented, along with NOEL's if relevant.

Table 1. Novel Synthetic AI's with ≥ 1 CORT Study Indicating "Adverse" Effect

Chemical Name	General Use	Study Type(s) with "Adverse" Effects Indicated
Flonicamid	Agricultural insecticide used on cotton, potatoes, pome fruit, and stone fruit	Mouse oncogenicity
Fluopicolide	Agricultural fungicide – cucumbers, bell peppers, celery	Mouse oncogenicity
Fluoxastrobin	Agricultural and ornamental fungicide – turf, potatoes, peanuts, tuberous vegetables	Rat oncogenicity
Metconazole	Agricultural and ornamental fungicide – stone fruits, tree nuts, peanuts, turf, ornamentals	Rat chronic, Dog chronic, Mouse Oncogenicity, Rat Reproduction
Metofluthrin	Mosquito repellent used in Urban outdoor areas	Dog chronic, Rat oncogenicity
Orthosulfamuron	Agricultural broadleaf herbicide – rice	Rat oncogenicity
Spirodiclofen	Agricultural miticide used on citrus, grapes, pome fruit, stone fruit, and tree nuts	Dog chronic, Rat oncogenicity, Mouse Oncogenicity, Rat Reproduction
Sulfosulfuron	Agricultural herbicide used on wheat, soybeans, potatoes, and turf	Rat chronic, Rat oncogenicity, Mouse oncogenicity
Tetraconazole	Agricultural fungicide – grapes, sugar beets	Mouse oncogenicity
Tribenuron-methyl	Technical herbicide	Rat reproduction
Triticonazole	Turf fungicide	Dog chronic

Table 2. AI's for Non-Food, Limited Exposure Uses, with Limited CORT Study Requirements

Chemical Name	General Use
Difenacoum	Rodenticide
Nicarbazin	Bird egg viability reducer used to control pigeons/geese
Tralopyril	Commercial and government use anti-fouling paint

Table 3. Novel Synthetic AI's with No"Adverse" Effects in CORT Studies

Chemical Name	General Use
Chlorantraniprole	Agricultural insecticide – tree fruits, ornamentals, cotton, grapes, potatoes, field crops
Cyazofamid	Agricultural fungicide used on cucurbits, potatoes, and tomatoes
Flubendiamide	Agricultural insecticide – eggplant, cucumbers, cabbage, almonds, peaches, cotton
Ipconazole	Agricultural use seed treatment fungicide – beets, amaranth, cotton, broccoli, sorghum
Mandipropamid	Agricultural fungicide – leafy vegetables, cucurbits, fruiting vegetables
Spinetoram	Agricultural insecticide used on bushberries, corn, pome fruit, bulb vegetables, fruiting vegetables, tree fruits, ornamentals, and turf
Metaflumizone	Non-crop insecticide – fire ants in turf and ornamentals

†RR = U.S. EPA designation of "reduced risk."

Table 4. AI's Substantially Similar to Existing Registered Compounds, Without New CORT Studies

Chemical Name	General Use
Boron oxide	Miticide used in homes and residents on pillows, mattress pads, and furniture stuffing
Chlorhexidine gluconate	Antimicrobial used on hard, non-porous surfaces
Copper citrate chelate	Algaecide used in potable water, reservoirs, ponds, canals
Copper gluconate chelate	Algaecide used in potable water, reservoirs, ponds, canals
Glyphosate, dimethylamine salt	Agricultural and industrial nonspecific herbicide
Potassium silicate	Broad-spectrum insecticide, miticide, fungicide – agricultural crops, ornamentals, turf

Table 5. AI's Returning with Lapsed Registrations, Without New CORT Studies

Chemical Name	General Use
3,7-Dimethyl-6-octen-1-ol	Agricultural us pheromone – mites on grapes, hots, tree fruits, nuts, ornamentals
Chitosan	Industrial use antimicrobial
Coumaphos	Bee hive miticide – Varroa mites
Flurprimidol	Plant growth regulator used on container grown ornamentals and trees
Metolachlor	Agricultural herbicide used on cotton, field crops, and row crops
Triallate	Agricultural herbicide used on wheat

FLONICAMID was flagged by DPR as a "high" priority chemical for risk assessment, due primarily to lung tumors in CD-1 mice (Ricerca Biosciences LLC, 2003).

1. There were well-defined increases in alveolar/bronchiolar adenomas (incidences and/or multiplicity) in both sexes at all dose levels tested in the primary study (29 to 261 mg/kg/day in males, 38 to 334 mg/kg/day in females).
2. Bronchiolar hyperplasia/hypertrophy were systematically increased over the entire dosage range.
3. Less dramatic, but plausibly treatment-related, increases in alveolar/bronchiolar carcinomas were significantly elevated at to 88 to 261 mg/kg/day in males, and at 334 mg/kg/day in females.
4. Dilated turbinate mucosal glands were elevated in high dose males only.
5. A supplementary lower-dose range 88-week study (Institute of Environmental Toxicology, Ibaraki, Japan, 2004) confirmed oncogenicity and pre-disposing alveolar/bronchiolar hyperplasia at that study's highest dose level (30 and 36 mg/kg/day for males and females, respectively). The next lower dose levels (10 and 12 mg/kg/day for males and females) was a NOEL for lung pathology.

Table 6. AI's Considered "Reduced Risk", Without Requirements for CORT Studies

Chemical Name	General Use
(E,E)-9,11-Tetradecadien-1-yl acetate	Agricultural and non-agricultural pheromone -Light Brown Apple Moth mating disruptant
(Z)-9-Dodecenyl acetate	Pheromone for forestry use to control pine shoot borers
Bacillus subtilis var. amyloliquifaciens, Strain FZB24	Agricultural fungicide - tree fruits, nuts, vegetables
Balsam Fir Oil	Rodent repellent
Chenopodium ambrosiodes near ambrosiodes	Agricultural and ornamental insecticide/miticide – grapes, garlic, lettuce, ornamentals
Coyote Urine	Home and industrial use vertebrate repellent
Fox Urine	Home and industrial use vertebrate repellent
Lavandulyl senecioate	Agricultural insect attractant – vine mealybug in grapes
Paecilomyces lilacinus Strain 251	Agricultural nematicide – tree fruits, nuts, leafy vegetables, turf
Pantoea agglomerans strain E 325, NRRL B-21856	Agricultural bactericide used to control fire blight on pears and apples
Pythium oligandrum DV74	Agricultural and greenhouse fungicide – field crops, ornamentals
Quillaja	Agricultural and ornamental nematicide, fungicide.
Sorbitol Octanoate	Agricultural and ornamental insecticide – fruits, vegetables, Christmas trees
Yeast extract hydrosylate from Saccharomyces cerevisiae	Agricultural fungicide used on citrus, cotton, and tomatoes
S-abscisic acid	Plant growth regulator used on ornamentals and grapes

†RR = U.S. EPA designation of "reduced risk."

METCONAZOLE was considered a "high" priority chemical for risk assessment, due to several findings, as follows.

1. Chronic rat (Fischer 344, 12 and 24-month sacrifice groups) study found necrotic inflammatory foci in livers of the two highest groups of males (13 and 44 mg/kg/day), but not in females (highest female dose was 54 mg/kg/day). Fatty vacuolation was observed in 13 to 44 mg/kg/day males, and in 54 mg/kg/day females.
2. Chronic dog study found lenticular degeneration in 3/3 males and in 2/4 females at 3000 ppm (111 and 114 mg/kg/day in males and females, respectively). No such lesions were observed at lower levels (which were 39 and 37 mg/kg/day, respectively).
3. Mouse (CD-1) oncogenicity study found markedly increased hepatocellular adenomas in males at the highest dose level (145 mg/kg/day). Females showed a marked hepatocellular adenoma response at the highest dose (179 mg/kg/day), plus high incidence of hepatocellular carcinomas at the same dose. Incidence of hepatocellular adenomas in 53 mg/kg/day females (4/51) appeared also to be meaningfully elevated over controls (0/50). There were sharp dose-responses in both sexes at the highest two dose levels for liver non-neoplastic lesions, most notably "sinusoidal hypercellularity/single cell necrosis/pigment" (41 to 145 mg/kg/day in males and 53-179 mg/kg/day in females).
4. A (CD) rat reproduction study was flagged for maternal toxicity (4 to 5 deaths per generation, typically at delivery). Findings were at 750 ppm (about 43-46 mg/kg/day during pre-mating periods). The next lower dose level (8.5 to 9.0 mg/kg/day for dams) was a NOEL for maternal, reproduction, and developmental toxicity effects.

METOFLUTHRIN was considered "high" priority for risk assessment, due to tremors in dogs and to oncogenicity in rats.

1. The dog chronic study was flagged for tremors in all males at 30 and 100 mg/kg/day, but not at the lowest dose of 10 mg/kg/day. Tremors were also seen in some females at 30 to 100 mg/kg/day, but not at 10 mg/kg/day. This appears to reflect acute or subacute responses which might be expected with this class of chemicals.
2. Wistar rats showed increased incidences of hepatocellular adenomas and carcinomas in both sexes at the highest dose levels (78 and 96 mg/kg/day in males and females, respectively). Numerical (non-significant) increases in these hepatocellular tumors at the next lower dose level (38 and 47 mg/kg/day, respectively) were plausibly also treatment-related. Modest increases in liver weights and in hepatocellular hypertrophy were evident at these levels.

FLUOPICOLIDE was flagged by DPR as a "moderate" priority chemical for risk assessment, due to hepatocellular tumors in C57BL/6 mice.

1. The basis for concern was hepatocellular adenomas at the highest dose only in both sexes (551 and 772 mg/kg/day in males and females, respectively).
2. Both sexes displayed elevated hepatocellular hypertrophy and elevated liver weights at the mid- and high-dose groups (64-551 mg/kg/day and 92-772 mg/kg/day in males and females, respectively). Overall NOEL's were 8 and 12 mg/kg/day in males and females.
3. The highest dose level in this study slightly exceeded targeted body weight effects for a maximum tolerated dose (MTD): body weight decrements for males and females were 22% and 20% at high dose level, with lower dose levels unaffected.

FLUOXASTROBIN was considered a "moderate" priority chemical for risk assessment, due to elevated uterine adenocarcinomas in Wistar rats at the highest dose level of 1083 mg/kg/day (3/50 in controls, vs. 10/49 in high dose females). There were no oncogenicity findings in females at the next lower dose level (181 mg/kg/day), nor in males at any dose level (highest dose level in males was 272 mg/kg/day).

1. Uterine glandular hyperplasia was elevated in 1083 mg/kg/day females.
2. There was an appreciable increase in the incidence and degree of "increased numbers of mast cells" in the mesenteric lymph nodes in 1083 mg/kg/day females, and in 272 mg/kg/day males.

SPIRODICLOFEN was prioritized as a high priority chemical for risk assessment due primarily to the multiple potential adverse effects and as an endocrine disruptor.

1. Testicular interstitial cell adenomas and uterine adenocarcinomas at 2500 ppm (LOEL,M: 110 mg/kg/day; F: 153 mg/kg/day) in rats [Combined rat chronic/oncogenicity study]. NOEL (M/F = 350 ppm or 14.7/19.9 mg/kg/day)
2. Leydig cell hypertrophy and vacuolation and bilateral focal tubular degeneration at 17.7 mg/kg/day (LOEL). Vacuolation of adrenal cortex at doses 150 ppm (LOEL, M/F: 4.43/4.74 mg/kg./day) and higher in both sexes. [Chronic dog feeding study]
3. Hepatocellular adenomas and carcinomas in male and female mice at 3500 (LOEL) and 7000 ppm. Testicular degeneration at 7000 ppm (1216 mg/kg/day). [Mouse oncogenicity study; NOEL (M/F) = 25 ppm or 4.1/5.1 mg/kg/day]
4. Testicular and epididymal atrophy and oligospermia were detected in 1750 ppm or 135 mg/kg/day treated rats. [Rat reproduction study] Parental NOEL = 350 ppm or 26 mg/kg/day.

ORTHOSULFAMURON was considered a "low" priority chemical for risk assessment, due to oncogenicity in rats.

Thyroid follicular cell adenoma incidence was significantly elevated in males at 500 and 1000 mg/kg/day. Females were unaffected at the same dose levels. Liver functional change (also in males only) was reflected by hepatocellular centrilobular hypertrophy (1000 mg/kg/day males) and centrilobular vacuolation (500 and 1000 mg/kg/day males).

A related supplementary study (Huntingdon Life Sciences, 2004) assessed relationships between liver and thyroid function in males. This study found increased TSH in 1000 mg/kg/day males, without changes in T3 or T4. At that dose level, liver weights were elevated, hepatic microsomal protein content was elevated, there was a profound increase in hepatic microsomal 7-pentoxyresorufin O-depentylase activity (31-fold), and a modest increase in hepatic microsomal UDP-glucuronosyltransferase. This study tends to support the supposition that thyroid tumors in the rat study were related to increased liver metabolic activity and associated thyroid enzyme turnover.

SULFOSULFURON was prioritized as a moderate priority chemical for risk assessment due to low incidence of urinary bladder tumors.

1. Urinary bladder adenomas (1/50) and urinary bladder carcinomas (1/50) in 5000 ppm treated female rats verses none (0/50) in control treated rats. Male rats exhibited increased incidences of urinary tract lesions and mineralization at 5000 ppm. [Combined rat chronic/oncogenicity study]. NOEL (M/F) = 24.4 mg/kg/day.
2. Benign urinary bladder tumors (5/50 vs. 0/50) at 7000 ppm (LOEL, 943.5 mg/kg/day) and urinary calculus formation in bladders at 3000 ppm (LOEL, 393.6 mg/kg/day) were noted in male mice. [Mouse oncogenicity study] NOEL (M/F) = 700 ppm or 93.4 mg/kg/day.
3. Similarly, histological lesions in urinary bladders in females (LOEL = 300 mg/kg/day) and urinary crystal formation (urolithiasis) and abnormal urinary crystals were observed in both sexes (LOEL (M/F) = 300/1

FLUOXASTROBIN was prioritized as a moderate priority chemical for risk assessment due to low incidence of urinary bladder tumors.

1. Urinary bladder adenomas (1/50) and urinary bladder carcinomas (1/50) in 5000 ppm treated female rats verses none (0/50) in control treated rats. Male rats exhibited increased incidences of urinary tract lesions and mineralization at 5000 ppm. [Combined rat chronic/oncogenicity study]. NOEL (M/F) = 24.4 mg/kg/day.
2. Benign urinary bladder tumors (5/50 vs. 0/50) at 7000 ppm (LOEL, 943.5 mg/kg/day) and urinary calculus formation in bladders at 3000 ppm (LOEL, 393.6 mg/kg/day) were noted in male mice. [Mouse oncogenicity study] NOEL (M/F) = 700 ppm or 93.4 mg/kg/day.
3. Similarly, histological lesions in urinary bladders in females (LOEL = 300 mg/kg/day) and urinary crystal formation (urolithiasis) and abnormal urinary crystals were observed in both sexes (LOEL (M/F) = 300/1000 mg/kg/day). [90 Day study in dogs] NOEL (M/F) = 100 mg/kg/day.

TETRACONAZOLE was prioritized as a moderate priority chemical for risk assessment based on the observation of hepatic tumors.

1. Histological changes in liver indicating that the liver is a target organ (LOEL M/F = 80 ppm 3.4/4.4 mg/kg/day) [Combined rat chronic/oncogenicity study]. NOEL (M/F) = 10 ppm or 0.4/0.6 mg/kg/day.
2. Male and female mice exhibited increased incidences of liver tumors at 800 ppm (LOEL M/F = 118/140 mg/kg/day) and 1250 ppm (217/224 mg/kg/day). Reduced spermatogenesis were noted in males treated these dose levels. [Mouse oncogenicity study] NOEL (M/F) = 10 ppm (1.4/1.6 mg/kg/day; based on elevated liver weights).

TRIBENURON - METHYL was prioritized as a moderate priority chemical for risk assessment based on the effects observed in organs associated with reproduction.

1. Increased amyloid deposits in testes and oligospermia in epididymides in males treated at 200 ppm (25 mg/kg/day, LOEL). [Mouse oncogenicity study] NOEL (M/F) = 20 ppm or 2.55 mg/kg/day.
2. Reduced number of pregnancies reported in rats (Parental NOEL = 50 mg/kg/day; LOEL = 250 mg/kg/day) and decreased pup weight and viability [Rat reproduction study] (offspring NOEL = 10 mg/kg/day).

CONCLUSION

Of 48 newly registered pesticidal AI's at California's DPR in 2007-2009, thirty-six were novel compounds, of which 18 were subjected to the full battery of toxicity studies mandated by FIFRA. Eleven had one or more CORT studies which DPR considered to indicate a "possible adverse effect" prioritized for risk assessment. Four were designated "high" priorities based on toxicity findings, dose-response relationships with their associated NOEL's, and plausible exposures based on proposed use patterns. Exposures to any of the novel new AI's appear to be sufficiently limited to warrant registration. Of the 4 AI's, metofluthrin is purchased simply as a clip-on repellant whereas spirodiclofen, flonicamid, and metconazole are marketed for agricultural or commercial uses, with appropriate worker protection standards and re-entry intervals. All products registered by DPR must also be registered by U.S. EPA. Thus materials registered in the past 3 years in California are consistent with the stewardship goals of the department.