



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DECISION MEMORANDUM

SUBJECT: Registration of Penoxsulam Herbicide.

FROM: Lois Rossi, Director
Registration Division (7505C)

*Lois Rossi
9/16/04*

TO: James Jones, Director
Office of Pesticides Programs (7501C)

REGISTRANT: Dow AgroSciences LLC

CHEMICAL: Penoxsulam
2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide

PRODUCTS: PENOXsulAM TECHNICAL, EPA FILE SYMBOL 62719-UOO
GF-881 MUP, EPA FILE SYMBOL 62719-LNE
GRASP* SC, (GF-443 SC SF), EPA FILE SYMBOL 62719-LNN
GRASP* GR, (GF-947 GRANULE SF), EPA FILE SYMBOL 62719-LNG
GRANITE* GR, (GF-947 GRANULE CA), EPA FILE SYMBOL 62719-LNR
GRANITE* SC, EPA FILE SYMBOL 62719-LRU

USE: Rice

This memorandum recommends that you concur on the conditional registration of and the establishment of corresponding tolerances for residues of the new herbicide in or on rice. Evaluation of data on penoxsulam suggest the criteria for conditional registration under FIFRA Section 3(c)(7)(C) have been met. Proposed tolerances for the parent compound, penoxsulam, can be established in or on the following commodities: rice grain at 0.02 ppm and rice straw at 0.5 ppm.

BACKGROUND

Dow AgroSciences petitioned (PP#3F6542) the Agency to establish a tolerance under 40 Code of Federal Regulation (CFR) 180 for the use of this new herbicide on rice. A notice of filing was published in the Federal Register on August 8, 2003 announcing that EPA was evaluating this petition. No comments were received for this FR Notice.

Penoxsulam is a acetolactate synthase (ALS) inhibitor herbicide, which can be applied post-emergence as a foliar spray on dry-seeded rice crops, or as either a foliar spray or a granular formulation on water-seeded rice crops in order to control broadleaf weeds, aquatic plants, and certain grasses.

SCIENTIFIC FINDINGS

EPA reviewed the submitted product chemistry, toxicology, residue chemistry, occupational exposure, ecological effects and environmental fate data. A summary of these assessments follows:

Health Effects Division's Review - Hazard Identification

In subchronic and chronic feeding studies in rats and dogs, the most sensitive target organ was the urothelium of the urinary system. Due to limited solubility in urine, penoxsulam (and/or its metabolites) formed crystals/calculi, which were regularly observed in the pelvis of the kidney and the lumen of the urinary bladder. These crystals/calculi apparently irritated the urothelium in these organs and following repeated dosing lead to numerous secondary effects which resulted in significant damage to the urinary system. In various studies, these secondary effects were manifested as altered clinical chemistry parameters (increased blood urea nitrogen), altered urinalyses parameters (increased urine volume, decreased urine specific gravity), increased absolute and relative kidney weights, gross pathological findings in the kidneys (calculi and roughened surface), and a variety of histopathological findings in the kidney and urinary bladder, particularly hyperplasia, inflammation and mineralization in the pelvic epithelium of the kidney and hyperplasia in the mucosa of the urinary bladder. Renal tubular degeneration was also sometimes observed. Although a treatment-related increased severity of chronic progressive glomerulonephropathy was observed in male rats, kidney damage observed in shorter-term studies was generally not exacerbated in longer-term studies. At similar and/or somewhat higher dose levels, mildly decreased body weight/body weight gain, often accompanied by decreased food consumption, were often observed in feeding studies in rats and dogs. In addition, in male rats, slightly decreased erythrocyte parameters (erythrocyte count, hemoglobin and hematocrit) were occasionally observed.

In subchronic and chronic feeding studies in mice, no effects of toxicological significance were observed in the 4-week, 13-week or 18-month feeding studies. In these studies, the only treatment-related effects observed at the dose levels tested were increased liver weights, increased hepatocellular hypertrophy, and related observations indicating stimulation of the liver microsomal enzyme system. These effects were considered to be an adaptive response to administration of the test material and not toxicologically significant adverse effects.

In a developmental toxicity study in rats, decreased body weight gain, decreased food consumption and increased kidney weights were observed in the dams. No developmental toxicity was observed. There was no increased quantitative or qualitative susceptibility of fetuses, as compared to dams, in this study. In a developmental toxicity study in rabbits, decreased body weight gain, decreased food consumption and clinical signs of toxicity (decreased/absent feces, or mucoid, soft, or abnormally colored feces) were observed in dams at the highest dose tested. One high dose doe died late in the study after exhibiting signs of clinical toxicity for several days. No developmental toxicity was

observed. There was no increased quantitative or qualitative susceptibility of fetuses, as compared to dams, in this study. In a 2-generation reproduction study in rats, microscopic lesions in the kidney were observed in the parental females at the mid and high dose levels. Preputial separation, an indicator of sexual maturation, was significantly ($p \leq 0.05$) delayed in mid and high dose F_1 males. The mean age at which preputial separation was attained for the control, low, mid, and high dose groups was 43.6, 44.0, 45.5, and 46.0 days, respectively. In addition, at the mid dose, 1 animal did not separate and at the high dose, 3 animals did not separate whereas all animals at the control and low doses did separate. The delay in preputial separation at the mid and high doses was considered to be a treatment-related effect. No other endpoints of reproductive toxicity or offspring growth and survival were affected by treatment. There was no increased quantitative or qualitative susceptibility of fetuses or offspring, as compared to adults, in this study.

No treatment-related neurotoxicity was observed in acute or chronic neurotoxicity studies in rats, or in any of the other available studies on penoxsulam. No systemic or dermal toxicity was noted in a 28-day dermal toxicity study in rats.

In a carcinogenicity study in rats, male and female rats were given penoxsulam in the diet for two years at dose levels of 0, 5, 50 or 250 mg/kg/day. In this study, there was a statistically significant increased incidence of malignant large granular lymphocyte (LGL) leukemia in each of the male treatment groups. The incidence was 24%, 60%, 58% and 60% in the control, low, mid and high dose level groups respectively. There was no dose response with all treated male groups having an approximately 2.5 fold increase over control animals. The incidence in the male treatment groups exceeded the conducting laboratory's historical control mean (28.5%) and range (16-40%), but fell within the National Toxicology Program (NTP) historical control data base of mean (50.5%) and range (32-74 %). There was also an increased severity (Stage 3) of LGL leukemia in all the treated male groups compared to the control group. There was no increase in incidence or severity of LGL leukemia for the treated female rats in this study. The dose levels in this study were considered to be adequate in male rats and marginally adequate in female rats to assess the carcinogenicity of penoxsulam. In a carcinogenicity study in mice, penoxsulam was administered in the diet for 18-months at dose levels up to 375 mg/kg/day in male mice and up to 750 mg/kg/day in female mice. An increased incidence of treatment-related tumors of any kind was not observed in the male or female mice. However, in males, the highest dose tested (375 mg/kg/day) was considered to be inadequate for carcinogenicity testing because no toxicologically significant adverse effects were observed at this dose (or in subchronic studies at doses up to 1000 mg/kg/day). In females, the highest dose tested (750 mg/kg/day) was considered adequate for carcinogenicity testing, but only because it was sufficiently close to the limit dose of 1000 mg/kg/day. Like males, no toxicologically significant adverse effects were observed in females at this dose (or in subchronic studies at doses up to 1000 mg/kg/day). The Cancer Assessment Review Committee (CARC) determined that although dosing in the males was not considered to be adequate, an additional mouse carcinogenicity study was not required because a repeat of the male mouse cancer study would have no impact on the regulation of penoxsulam. Penoxsulam was classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" and, therefore, quantification of human cancer risk is not required.

Technical grade penoxsulam did not demonstrate any mutagenic potential in a battery of four mutagenicity studies. There is not a concern for mutagenicity resulting from exposure to penoxsulam.

In a metabolism study in rats, ¹⁴C-penoxsulam was rapidly and nearly completely absorbed at the low dose of 5.0 mg/kg, but at the high dose of 250 mg/kg, there was evidence that absorption was largely incomplete (i.e. absorption was saturated). Both gender and dose affected the excretion pattern. At the low dose, the major route of excretion of radioactivity was via the feces in males and via the urine in females. At the high dose, radioactivity was predominantly excreted via the feces in both sexes. A significant enterohepatic circulation was observed, particularly in males. Most (>90%) of the administered dose was excreted within 36-48 hours. There was negligible radioactivity in tissues at 7 days and no evidence of accumulation in any tissue/organ. Although numerous metabolites were revealed in the urine, feces and bile, nearly all were <1% of the administered dose. Parent compound and a 2-hydroxyphenyl derivative were the major compounds in urine and feces.

HED concluded that the toxicology database for penoxsulam is complete for FQPA purposes, and a database uncertainty factor is not needed for penoxsulam (i.e., removed or 1x). HED also concluded that there is not a concern for neurotoxicity resulting from exposure to penoxsulam. No evidence of neurotoxicity was observed in the acute or chronic neurotoxicity studies in rats or in any of the subchronic or chronic feeding studies in rats, mice or dogs. HED determined that no Special FQPA Safety Factor is needed (i.e. 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity.

Endpoints were selected for acute and chronic dietary exposure, short- and intermediate-term incidental oral exposure and short-, intermediate- and long-term dermal and inhalation exposure. There were no treatment-related effects observed in any of the available toxicity studies on penoxsulam that could be considered to have resulted from a single dose of the test material, therefore no acute endpoint was established for penoxsulam. The chronic dietary endpoint is based on multifocal hyperplasia of the pelvic epithelium of the kidney in a 1-year chronic feeding study in dogs (chronic PAD = 0.147 mg/kg/day). The incidental oral exposure short- (1-30 days) and intermediate- (1-6 months) term endpoint is based on histopathologic changes in kidneys in a 13-week feeding study in dogs (NOAEL = 17.8 mg/kg/day, MOE = 100). The dermal absorption factor was estimated to be 50% as an upper bound estimate for all dermal exposure scenarios. The absence of dermal, systemic, neuro or developmental toxicity concerns resulted in there being no selection of a dermal short-term (1-30 days) endpoint. The dermal intermediate-term (1-6 mo) endpoint is based on histopathologic changes in kidneys in a 13-week feeding study in dogs (NOAEL = 17.8 mg/kg/day, MOE = 100). The dermal long-term (>6 mo) endpoint based on multifocal hyperplasia of the pelvic epithelium of the kidney in a 1-year chronic feeding study in dogs (NOAEL = 14.7 mg/kg/day, MOE = 100). The inhalation exposure short- (1-30 days) and intermediate- (1-6 months) term endpoint is based on histopathologic changes in kidneys in a 13-week feeding study in dogs (NOAEL = 17.8 mg/kg/day, MOE = 100). The inhalation long-term (>6 mo) endpoint is based on multifocal hyperplasia of the pelvic epithelium of the kidney in a 1-year chronic feeding study in dogs (NOAEL = 14.7 mg/kg/day, MOE = 100).

FQPA Decision

HED concluded that no Special FQPA Safety Factor is needed (i.e. 1x) since there are no residual uncertainties for pre- and/or post-natal toxicity. The penoxsulam risk assessment team evaluated the quality of the hazard and exposure data; and, based on these data, recommended that the special

FQPA SF be reduced to 1x. The recommendation is based on the following:

There was no toxicologically significant evidence observed of neurotoxicity in either the acute or chronic neurotoxicity study.

No definitive quantitative or qualitative susceptibility was observed in either of the developmental rat or rabbit studies

Significant dose-related effects in the two-generation reproduction study were limited to the delay in preputial separation. No other endpoints of reproductive toxicity or offspring growth and survival were affected by treatment.

The *chronic* dietary food exposure assessment utilizes proposed tolerance level residues and 100% CT information for all commodities. By using these conservative assessments, actual and chronic exposures/risks will not be underestimated.

The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

Chronic Dietary Exposure

The chronic dietary analysis for penoxsulam was conducted using the Lifeline™ Model Version 2.0, which uses food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CFSII) from 1994-1996 and 1998. The assessment was based on tolerance level residues and 100 %CT for the requested use on rice. This conservative (Tier 1) analysis indicates that chronic risk from the dietary exposure to penoxsulam from the requested use did not exceed HED's level of concern for the U.S. population or any population subgroup. All exposures were determined to be <1% cPAD for the U.S. population and all sub populations of interest.

Drinking Water Exposure

EFED determined Tier 1 Estimated Drinking Water Concentrations (EDWCs) for ground and surface water for the postemergence herbicide, penoxsulam, when used on rice crops. The degradates which are to be included in the risk assessment are BSTCA, 2-amino TCA, 5-OH-XDE-638, SFA, sulfonamide, and 5,8-diOH. Applying the method outlined in the current EFED interim policy for calculating both the Tier I estimated ecological effects concentrations (EECs) and EDWCs resulting from the use of pesticides on rice crops produced an upper bound screening estimation, using the lowest K_d value (0.13) for a non-sand soil, of 45 ppb (ug/L) in paddy waters. The estimated EEC calculated in accordance with the EFED interim policy should be used for both acute and chronic EECs, as well as for both aquatic ecological risk assessments and for EDWCs in human health risk assessments. Modeling ground water concentrations using the standard Tier 1 model, SCI-GROW, estimated combined residue EDWCs of 5.86 ppb (ug/L). Ground water concentrations were estimated for parent-only at 0.67 ppb (ug/L). However, EFED does not regard ground water

contamination from a pesticide applied to rice to be a significant route of dissipation. The calculated chronic Drinking Water Level of Comparison (DWLOC) for infants and children (ages 1 - 12 years old) is 1.5 ppm, for youths (ages 13 - 19 years old) and adults (20 - 50+ years old) it is 5.1 ppm, and females (ages 13 - 49 years old) it is 4.4 ppm.

Endocrine Disruption

For penoxsulam, effects which indicate potential endocrine disruption include kidney lesions (crystals) in female rats and delay in preputial separation in male rats. When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, penoxsulam may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

Risks to Pesticide Applicators and Handlers

Besides a technical product, Penoxsulam Technical (EPA File Symbol 62719-UOO), and a manufacturing use product, GF-881 MUP (EPA File Symbol 62719-LNE), Dow has requested registration of four end-use products, two liquid formulations and two granular formulations, for selective postemergence weed control in rice. The proposed labels for the Grasp SC (GF-443 SC SF) liquid (EPA File Symbol 62719-LNN) and Grasp GR (GF-947 GRANULE SF) granular (EPA File Symbol a62719-LNG) formulations indicates use in Arkansas, Florida, Louisiana, Mississippi, Missouri, and Texas. The proposed labels for the Granite GR (GF-947 GRANULE CA) granular (EPA File Symbol 62719-LNR) formulation and Granite SC liquid (EPA File Symbol 62719-LRU) formulations indicate use in California only.

The end-use products as liquid formulations (EPA File Symbol 62719 - LNN and 62719-LRU) are 21.7 % active ingredient (ai) or 2.0 lb ai per gallon. They may be applied one time per year by aerial or ground equipment at a maximum rate of 0.044 lb a.i./A. It may not be applied through any type of irrigation equipment. It may be applied to water seeded rice or dry seeded rice. The application is to be made between the 1 leaf stage of crop growth and 60 days before harvest. The label requires the use of an agriculturally approved crop oil concentrate at a rate of 1 quart per acre or 2.5 % (Granite SC label) per application. Depending upon cropping practices, the label includes specific water management directions relative to an application of penoxsulam.

The granule products (EPA File Symbol 62719 - LNG and 62719-LNR) are used for selective weed control in water-seeded rice. It is a 0.24 % granular formulation. The proposed products are designated for use at a rate of 18.5 lb (0.044 lb a.i.) per acre. They may be applied one time per year in ground or aerial equipment. The application should occur between the 1 leaf stage of rice growth and 60 days prior to harvest. For optimum performance, fields should be flooded to a depth of 2 to 4 inches prior to application and water maintained at 2 to 4 inches in depth for 10 days following application.

All four end-use products have a 12 hour restricted entry interval (REI). All proposed labels require pesticide handlers to wear long sleeved shirt, long pants and shoes plus socks.

A MOE of 100 is adequate to protect occupational pesticide handlers. All estimated MOE's are > 100

except for intermediate-term exposures to mixer/loaders not using gloves with liquid, open-pour loading in support of aerial operations (at either 1200 acres per day or 350 acres per day). Loaders using liquid open-pour in support of aerial operations (and who may experience intermediate-term exposures) should wear protective gloves. Generally speaking, HED advises the use of protective gloves for mixer/loaders. Otherwise, the proposed uses do not exceed HED's level of concern.

Environmental Fate and Effects Division's Review

Ecotox

The results of the screening-level risk assessment suggest that penoxsulam will not pose a threat to aquatic or terrestrial animals, however, this conclusion must be tempered by the fact that testing has not been conducted on several major degradates. Because penoxsulam is an ALS inhibitor, it is not anticipated that it would pose a threat. Nevertheless, penoxsulam is a member of the sulfonamide family which includes antimicrobial agents.

Penoxsulam application at proposed maximum levels does pose a potential risk to aquatic and terrestrial plants. Specifically, seedling emergence risk quotients for terrestrial plants exceeded Levels of Concern for eight out of ten crops studied, although half of those exceedances resulted from a failure to test at a sufficiently high rate. That is the calculation of the RQ's defaulted to using the highest dose tested, even when the dose indicated no adverse effects. The peak RQ for monocots was 44 for non-endangered species and 120 for endangered terrestrial plants based on studies with onions. The peak RQ for dicots was 15 for non-endangered species and 41 for endangered species, both based on studies with sugar beets. These endpoints are applicable to the Tier 1 estimate for terrestrial plants in terrestrial and semi-aquatic settings from application of either the liquid or granular formulation.

Vegetative vigor risk quotients for terrestrial plants resulted in exceedances for eight out of ten crops for endangered species and six out of ten crops for non-endangered species. The peak RQ for dicots was 13 for non-endangered plants based on studies with the soybean and of 41 for endangered species based on studies with the soybean, sugar beet, and tomato. The peak RQ for monocots was 2.9 for non-endangered species and 120 for endangered plants, both based on studies with ryegrass. Shoot weight was the sensitive endpoint for all of these risk quotients. These endpoints form the Tier 1 estimates for non-target, terrestrial plant exposure due to spray drift.

For aquatic plants, the vascular plant RQs are based on the response of Duckweed (*Lemna gibba*). It generates an RQ of 15 for non-endangered species and of >45 of endangered species. For non-target, non-vascular aquatic plants, the green alga (*Selenastrum capricornutum*) had an RQ of 9 for endangered species when stressed with technical grade penoxsulam and an RQ of 5 for endangered species when stressed with the end-use product GF-443. risk quotients (RQs) for the following taxonomic groups exceed levels of concern for the screening-level risk assessment. These estimates apply to all application practices.

Any concern for endangered plants will be mitigated by the addition of buffer zones and drift control strategies to product labels.

Environmental Fate

Penoxsulam is expected to be very mobile, but not persistent, in either aqueous or terrestrial environments. Penoxsulam exists almost exclusively in a disassociated state at pH values normally found in rice paddy water, but not in terrestrial environments where lower pH values may be found. Penoxsulam degrades by two different transformation mechanisms, producing thirteen different identified transformation products, for photolytic and biotic degradation. Six of these transformation products reached peak concentrations at study termination, indicating a greater degree of persistence than penoxsulam and a potential to reach concentrations even greater than those reported at study termination.

Persistence- Penoxsulam is not expected to be persistent in the environment. Aqueous photolysis and aerobic degradation are expected to be the major routes of dissipation. In aqueous environments, penoxsulam is expected to be stable to hydrolysis, but to dissipate rapidly through aqueous photolysis in clear shallow waters, and more slowly through biotic degradation when sunlight has a limited ability to penetrate turbid waters, or when waters are shaded by trees, riparian vegetation, and/or crop canopies. In terrestrial environments, penoxsulam is expected to dissipate through soil photolysis and biotic degradation. Considering its low vapor pressure and Henry's Law constant, volatilization from soil and water is not expected to contribute significantly to the dissipation of penoxsulam the environment. Penoxsulam also has low potential to bioaccumulate in fish.

Mobility- Penoxsulam is expected to be very mobile in both aqueous and terrestrial environments, not binding strongly to either soil or sediment. Submitted mobility data for three penoxsulam degradation products (3-[[[2-(2,2-Difluoroethoxy)-6-(trifluoromethyl)phenyl]-sulfonyl]amino]-1H-1,2,4-triazole-5-carboxylic acid (BSTCA), 5-OH-penoxsulam, and 2-(2,2-Difluoroethoxy)-N-1H-1,2,4-triazole-3-yl-6-(trifluoromethyl) benzenesulfonamide (BST)) indicate environmental mobility roughly equivalent to the parent compound. However, there are no data regarding the mobility of the remaining transformation products or of combined parent/degrade residues. Penoxsulam has low volatility indicating that atmospheric transport is, at best, a very minor route of transportation.

Aquatic Concentrations- Surface water contamination by penoxsulam is assumed to occur through drift or designed release to a stream or pond. Unlike terrestrial row crops, the major growth and development phases for a rice crop take place in a flooded field, or paddy. A paddy is typically designed to capture and maintain a uniform depth of irrigation (flood) water. This design minimizes aquatic transport to ground water via levee overflow, breaching, and leaching (also known as deep percolation).

Transformation Products- Data are not available to fully characterize the complex, potential degradation pathways of penoxsulam. Submitted laboratory studies demonstrate that penoxsulam transforms by competing mechanisms, through several generations of degradation products. Examination of the specific transformation products formed in the submitted laboratory studies, suggests that the more rapid photolytic transformation proceeds primarily through cleavage of the parent molecule on, or adjacent to, the sulfonamide bridge. The slower biotic degradation pathway proceeds primarily through fragmentation of the pyrimidine ring or its residues.

Six of the thirteen identified transformation products reached peak concentrations at study

termination. These six compounds are potentially more persistent than the parent compound, and would probably have reached even greater concentrations with time. Only limited fate data are available for the penoxsulam transformation products, including the six penoxsulam degradates which the Health Effects Division determined to be of human toxicological concern: BSTCA, 2-amino-1,2,4-triazole carboxylic acid (2-amino TCA), 5-OH-penoxsulam, 2-(2,2-Difluoroethoxy)-N-(trifluoromethyl)-benzenesulfonamide (SFA), 2-(2,2-Difluoroethoxy)-6-(trifluoromethyl)-benzenesulfonamide (sulfonamide), and 5,8-di-OH-penoxsulam.

OUTSTANDING DATA

Residue Chemistry

The final report of the ongoing storage stability study must be submitted in support of any future food uses. Storage stability data for future uses will require the receipt and acceptance of the final rice report as well as any data required for the additional use.

Environmental Fate

Seed germination/seeding emergence studies, vegetative vigor studies, and an aquatic plant growth study using Duckweed with the degradates, BSA, 2-amino-TP, TPSA, BSTCA methyl, BSTCA, 2-amino-TCA, 5-OH-penoxsulam, SFA, sulfonamide, 5,8-di-OH and 5-OH, 2 amino TP. The registrant submitted a large set of studies, including studies on penoxsulam's large number of degradates. There are two studies that have been identified as outstanding.

In addition several of the studies with degradates need to be repeated or done for additional organisms. EFED cannot determine which degradates or which organisms until the Health Effects Division completes its analysis of the effects of these chemicals. EFED is concerned that certain degradates that remain in the environment at relatively high concentrations will increase the effect of the parent. Some of these degradates resemble the parent and may be the active moiety.

PUBLIC INTEREST FINDING

Penoxsulam use on rice was determined to be a reduced risk pesticide due to its favorable human health risk profile when compared to registered ACCase alternatives and a similar or favorable ecotoxicity profile when compared to other ALS-inhibitors registered for use on rice.

GOVERNMENT PERFORMANCE AND RESULTS ACT OF 1993 (GPRA)

GPRA activities associated with this action are Registration of Safer Chemicals and Other Registration Actions (Subobjectives 3.1.1, 3.1.3, and 4.1.1,).

