## 5.5 Buprofezin (173)

### TOXICOLOGY

Buprofezin is the ISO-approved name for (*Z*)-2-*tert*-butylimino-3-isopropyl-5-phenyl-1,3,5-thiadiazinan-4-one (IUPAC), CAS number 69327-76-0. Buprofezin is an insecticide that acts by the inhibition of chitin synthesis.

Buprofezin was previously evaluated by JMPR in 1991, 1999 and 2008. In 1991 an ADI of 0–0.01 mg/kg bw was established based on a NOAEL of 0.9 mg/kg bw per day identified in a two-year study in rats and with a safety factor of 100. In 1999 JMPR considered that the establishment of an ARfD was unnecessary. In 2008 the JMPR Meeting concluded on an ADI of 0–0.009 mg/kg bw, based on the same study and NOAEL as the 1991 evaluation. The 2008 JMPR established an ARfD of 0.5 mg/kg bw based on the NOAEL of 50 mg/kg bw per day for ataxia in a 13-week dog study.

Buprofezin was re-evaluated at the present Meeting at the request of CCPR to support additional MRLs and in response to a concern raised by a Codex member. This concern related to the production of aniline from residues of buprofezin during the processing of commodities. New information, not previously evaluated, included an in vivo gene mutation study of aniline in transgenic rats and published literature on the toxicity and carcinogenic mode of action of aniline. There were no new data submitted on buprofezin. This evaluation focuses on the available data for aniline, in particular that for carcinogenicity, genotoxicity and relevance to human exposures.

The new gene mutation study contained a statement of compliance with GLP and complied with the applicable OECD test guideline. The review used both primary sources of information and reviews from national/international organizations. The papers from the published literature did not provide evidence that they complied with GLP or national or international test guidelines.

#### *Toxicology data on metabolites and/or degradates.*

##### *Biochemical aspects*

Aniline is extensively absorbed when administered orally to rats (ca 90% at 50 or 250 mg/kg bw) and mice (ca 70% at 100 or 500 mg/kg bw), based on 0–24 h urine samples.

Peak plasma radioactivity levels in rats dosed with $^{14}$C-aniline at 10, 30 or 100 mg/kg bw were 0.5, 1 and 2 h respectively. Following oral dosing of $^{14}$C-aniline to rats, at 100 mg/kg bw for one day, the highest concentration of radiolabel was detected in erythrocytes (25 µg equiv./g), with lower levels (0.4– 4 µg equiv./g) in plasma, liver, spleen, kidney, lung and heart. Following 10 days dosing at 100 mg/kg bw per day, radioactivity in spleen was 12 times higher than after one day, other tissues had increases of 1.8- to 3.8-fold. Covalent binding of radioactivity to proteins was six times higher in the spleen than in the liver.

Excretion is rapid in rats and humans with a half-life of approximately three hours.

The metabolism of aniline is via *N*-hydroxylation, *N*-acetylation and/or hydroxylation of the phenyl ring, followed by conjugation with glucuronic acid or sulfate. The excretory pathway in rats relies extensively on sulfate conjugation, which is reported to become saturated at doses above 50 mg/kg bw. In mice, conjugation is with glucuronic acid and this pathway is reported not to become saturated. The proportion of *N*-hydroxylation or *N*-acetylation is reported to vary with species, sex and, in humans, acetylation phenotype. The *N*-hydroxy metabolite, *N*-hydroxyaniline (phenylhydroxylamine), is reported to be oxidized to nitrosobenzene in erythrocytes, leading to the production of methaemoglobin (MetHb) and a sulfuric acid amide adduct of haemoglobin.

##### *Toxicological data*

Aniline has an $LD_{50}$ of 442 mg/kg bw in rats and an $LC_{50}$ of 1 mg/L in rats. Aniline is slightly irritating to the skin, severely irritating to the eye and exhibits skin sensitizing potential in guinea pigs and

humans.

In an eight-week range-finding study, mice received aniline hydrochloride at 0, 100, 300, 3000 or 10 000 ppm in the diet weeks (equivalent to aniline exposures of 11, 32, 324 or 1080 mg/kg bw per day). At 3000 ppm (equivalent to 324 mg/kg bw per day) and above, all mice had dark, granular and enlarged spleens. There is insufficient information to determine a NOAEL.

In an eight-week range-finding study, rats received aniline hydrochloride at 0, 100, 300, 3000 or 10 000 ppm in the diet (equivalent to aniline exposures of 7, 21, 210 or 700 mg/kg bw per day). At 3000 ppm (equivalent to 210 mg/kg bw per day) and above, all rats had dark, granular and enlarged spleens. There is insufficient information to determine a NOAEL.

In a repeat dose toxicity study, male rats received aniline hydrochloride at variable concentrations in the diet for one or four weeks to provide nominal aniline exposures of 0, 4, 12 or 40 mg/kg bw per day. The LOAEL in this study was 4 mg/kg bw per day, the lowest dose tested, based on vascular congestion of the spleen and haemoglobin (Hb) adducts.

Aspects of the repeat dose toxicity of aniline were investigated in a 28-day study of genotoxicity. Groups of transgenic Fischer 344 Big Blue® male rats were administered aniline at doses of 0, 25, 50 or 100 mg/kg bw per day, once daily via oral gavage. A NOAEL could not be determined from this study as changes in blood (increased MetHb and reticulocytes) and spleen (increased weight and iron deposition) were noted at all dose levels. The LOAEL was 25 mg/kg bw per day.

In a long-term toxicity and carcinogenicity study, mice received aniline hydrochloride at 0, 6000 or 12 000 ppm in the diet for 103 weeks followed by a four-week observation period. Doses were equivalent to aniline exposures of 600 or 1200 mg/kg bw per day. Investigation of general toxicity was limited, and a NOAEL for general toxicity could not be derived. The NOAEL for carcinogenicity was 12 000 ppm (equivalent to 1200 mg/kg bw per day), the highest dose tested.

In a long-term toxicity and carcinogenicity study, rats received aniline hydrochloride at 0, 3000 or 6000 ppm in the diet for 103 weeks followed by a four-week observation period. Doses were equivalent to aniline exposures of 105 or 210 mg/kg bw per day. Tumours of the spleen (fibrosarcoma, stromal sarcoma, haemangiosarcoma, osteogenic sarcoma) were increased in both male groups and high-dose females. The LOAEL for carcinogenicity was 3000 ppm (equivalent to 105 mg/kg bw per day) the lowest dose tested, based on increases in tumours of the spleen in males at this dose level. The LOAEL for toxicity is 3000 ppm (equivalent to 105 mg/kg bw per day) the lowest dose tested, based on papillary hyperplasia of the spleen in females. A review of the histopathology slides confirmed the carcinogenicity and general toxicity to the spleen.

In a second long-term toxicity and carcinogenicity study, in the same strain, rats received aniline hydrochloride in the diet at variable concentrations, for two years to give nominal exposures of 7, 22 or 72 mg/kg bw per day. Tumours of the spleen were increased in males in the mid- and high-dose groups, but not in females. The LOAEL for general toxicity was 7 mg/kg bw per day, based on reduced erythrocyte counts, and pathological changes in the spleen at this dose level. The NOAEL for carcinogenicity is 7 mg /kg bw per day. The Meeting calculated $BMDL_{10}$ values for all spleen tumours of 38.6 mg/kg bw per day and 43.4 mg/kg bw per day for stromal sarcoma of the spleen.

The Meeting concluded that aniline is not carcinogenic in mice but carcinogenic in rats.

Aniline has been investigated in a wide range of in vitro and in vivo genotoxicity studies of varying quality. It was negative in bacterial mutation assays but some positive results, with and without metabolic activation, have been reported in in vitro mammalian cell gene mutation assays and clastogenicity studies in vitro and in vivo. The most consistent finding was of clastogenicity, which was supported by colony size analysis in the mouse lymphoma gene mutation assays. Low levels of aniline-derived radioactivity binding to DNA in some organs were seen at high doses of aniline (500 mg/kg bw), possibly via the production of reactive intermediates such as *N*-hydroxyphenylamine and *p*-hydroxyacetanilide. In a 28-day study of genotoxicity, groups of transgenic Fischer 344 Big Blue® male rats were administered aniline at doses of 0, 25, 50 or 100 mg/kg bw per day, via oral gavage. A dose-related increase in micronucleated erythrocytes from the peripheral blood was seen at

four and 29 days, together with increases in erythropoiesis and numbers of reticulocytes. There was no increase in *cII* mutants in the spleen, liver or bone marrow at any dose level.

There is evidence that aniline is clastogenic in vitro and in vivo but not mutagenic in vivo.

The Meeting considered that the clastogenicity of aniline was due to a mechanism secondary to reactive oxygen production and that a threshold would apply. The Meeting concluded therefore that aniline is unlikely to be genotoxic at estimated dietary exposure levels.

### *The mode of action for formation of spleen tumours*

The MOA behind the spleen tumours has been investigated. The meeting considered that the low level of DNA binding of aniline metabolites was unlikely to be the cause for the significant increase of spleen tumours in male rats observed at moderate doses. This is supported by absence of tumour response in other organs. A range of studies support the proposed mode of action based on redox-associated damage to erythrocytes, increase in Heinz bodies, and stimulation of erythropoiesis. The damaged erythrocytes are removed by the spleen, which leads to an increase in free iron deposition in the spleen, production of reactive oxygen species, protein oxidation and lipid peroxidation. These changes result in a progression of pathological lesions in the spleen from congestion, capsulitis, to hyperplasia and tumours. Although the available studies do not address all the tumour findings (e.g. sensitivity of male rats versus females and no splenic tumours in mice), the proposed mode of action is plausible and taken with the absence of mutations in the spleen in the in vivo gene mutation study, it supports a threshold mode of action secondary to erythrocyte damage. Humans exposed to aniline produce significant levels of MetHb (a biomarker of redox damage) therefore the mode of action is of relevance to humans.

The Meeting concluded that, based on the absence of gene mutations in the spleen and a clear threshold for splenic tumours by the established mode of action, aniline is unlikely to be carcinogenic to humans at estimated dietary exposure levels.

In a study of developmental and postnatal toxicity, rats were dosed with aniline hydrochloride by gavage at 0, 7, 21 or 70 mg/kg bw per day (as aniline) on days 7– 20 of gestation. Dams were allowed to deliver naturally (up to day 24 of gestation) and then nurse the pups until PND 30. The NOAEL for maternal toxicity was 21 mg/kg bw per day, based on increases in MetHb and relative spleen weights at 70 mg/kg bw per day. The NOAEL for offspring toxicity was 7 mg/kg bw per day, based on increased pup mortality at 21 mg/kg bw per day.

In a study of developmental toxicity, rats were dosed with aniline hydrochloride by gavage at 0, 7, 21 or 70 mg/kg bw per day on days 7–20 of gestation. The LOAEL for maternal toxicity was 7 mg/kg bw per day, the lowest dose tested, based on increased relative spleen weights at this dose level. The NOAEL for embryo/fetal toxicity was 70 mg/kg bw per day, the highest dose tested.

The Meeting concluded that aniline is not teratogenic in rats.

### *Microbiological data*

No data available.

### *Human data*

Human volunteers received an oral dose of aniline of 5, 15, 25, 35, 45, 55 or 65 mg/person per day on three consecutive days. Volunteers exposed to 5 or 15 mg of aniline had small, not statistically significant, increases in MetHb levels (< 2%). Volunteers receiving 25 mg to 55 mg aniline had statistically significant increases in MetHb (2.5% to 7%). The volunteer receiving 65 mg of aniline had a peak MetHb level of 16% at 2 h post-dose but this had returned to normal at the 3 h sample, showing rapid recovery. The NOAEL was 15 mg/person (equivalent to 0.2 mg/kg bw per day) based on significant increases in MetHb at 25 mg/person (equivalent to 0.35 mg/kg bw per day).

The excess of bladder cancer deaths observed in clusters of cases of workers in the aniline-based dye industry has been attributed to exposure to chemicals other than aniline. Epidemiological studies of workers exposed to aniline, but not to other known bladder carcinogens, have shown little

evidence of increased risk. A mortality study of 342 men employed in the manufacture of organic dyes, in which two of the three processes involved aniline as a raw material, showed no death from bladder cancer.

## Toxicological evaluation

The Meeting established an ADI of 0–0.02 mg/kg bw on the NOAEL of 0.2 mg/kg bw per day for increases in methaemoglobin levels in a human volunteer study. As this observation was made in humans no interspecies safety factor was necessary and a safety factor of 10 was applied. There is a margin of 1100 between the upper bound of the ADI and the LOAEL for spleen tumours in the rat.

An ARfD of 0.02 mg/kg bw was established on the same basis as the ADI.

A toxicological monograph addendum was prepared.

### *Levels relevant to risk assessment of aniline*

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | Two-year study of toxicity and carcinogenicity[a] | Toxicity | -[b] | -[b] |
| | | Carcinogenicity | 12 000 ppm, equivalent to 1200 mg/kg bw per day[c] | - |
| Rat | 28-day oral toxicity study [a] | Toxicity | - | Variable ppm to give 4 mg/kg bw per day[d] |
| | Two-year studies of toxicity and carcinogenicity[a], | Toxicity | - | Variable ppm to give 7 mg/kg bw per dayd |
| | | Carcinogenicity | Variable ppm to give 7 mg/kg bw per day | Variable ppm to give 22 mg/kg bw per day |
| | One-generation study of developmental and post-natal toxicitye | Reproductive toxicity | -[b] | -[b] |
| | | Parental toxicity | 21 mg/kg bw per day | 70 mg/kg bw per day |
| | | Offspring toxicity | 7 mg/kg bw per day | 21 mg/kg bw per day |
| | Developmental toxicity study[b] | Maternal toxicity | - | 7 mg/kg bw per day[d] |
| | | Embryo and fetal toxicity | 70 mg/kg bw per day[c] | - |
| Rabbit | No data | | | |
| Dog | No data | | | |
| Human | Three-day study of toxicity[e] | MetHb production | 0.2 mg/kg bw per day | 0.35 mg/kg bw per day |

[a] Dietary administration

[b] Inadequate investigation

[c] Highest dose tested

[d] Lowest dose tested

[e] Gavage administration

*Acceptable daily intake (ADI) for aniline*

0–0.02 mg/kg bw

*Acute reference dose (ARfD) for aniline*

0.02 mg/kg bw

### *Information that would be useful for the continued evaluation of aniline*

Results from epidemiological, occupational health and other such observational studies of human exposure.

### *Critical end-points for setting guidance values for exposure to aniline*

| | |
|---|---|
| ***Absorption, distribution, excretion and metabolism in mammals*** | |
| Rate and extent of absorption | Rapid ($T_{max}$ 2 h) and extensive (70–90% based on urine) |
| Dermal absorption | No data |
| Distribution | Extensive; highest concentrations in RBC, liver, kidney, spleen |
| Potential for accumulation | High in spleen |
| Rate and extent of excretion | Rapid (half-life 3 h in rats, mainly in urine) |
| Metabolism | *N*-acetylation, *N*-hydroxylation, *C*-hydroxylation; conjugation with glucuronic acid or sulfate. |
| Toxicologically significant compounds in animals and plants | Aniline |
| ***Acute toxicity*** | |
| Rat, $LD_{50}$, oral | 442 mg/kg bw |
| Rat, $LC_{50}$, inhalation | 1 mg/L |
| Rabbit, dermal irritation | Slight irritant |
| Rabbit, ocular irritation | Severe irritant |
| Guinea pig/human, dermal sensitization | Evidence of sensitization |
| ***Short-term studies of toxicity*** | |
| Target/critical effect | MetHb formation, erythrocyte damage, toxicity to spleen |
| Lowest relevant oral LOAEL | 4 mg/kg bw per day (rats) |
| Lowest relevant oral NOAEL | 0.2 mg/kg bw per day (humans) |
| ***Long-term studies of toxicity and carcinogenicity*** | |
| Target/critical effect | Carcinogenic to the spleen of rats<br>MetHb formation, erythrocyte damage, toxicity to spleen |
| Lowest relevant LOAEL (toxicity) | 7 mg/kg bw per day, lowest dose tested (rats) |
| Carcinogenicity | Unlikely to pose a carcinogenic risk to humans at estimated dietary exposure levels. |
| Carcinogenicity lowest NOAEL [a] | 7 mg/kg bw per day (rats) |
| ***Genotoxicity*** [a] | Clastogenic in vitro and in vivo. Not mutagenic in vivo in the spleen, liver or bone marrow. Unlikely to be genotoxic at estimated dietary exposure levels. |
| ***Reproductive toxicity*** | |

| | |
|---|---|
| Target/critical effect | Reduction of pup survival |
| Lowest relevant reproductive NOAEL | 7 mg/kg bw per day (rats) |
| ***Developmental toxicity*** | |
| Target/critical effect | None |
| Lowest relevant NOAEL | 70 mg/kg bw per day, highest dose tested (rats) |
| ***Neurotoxicity*** | No data |
| ***Immunotoxicity*** | No data |
| ***Studies on toxicologically relevant metabolites*** | No data |
| ***Human data*** | NOAEL for MetHb in a three-day gavage study in volunteers is 0.2 mg/kg bw per day<br>Reports of bladder cancer in workers exposed to multiple aromatic amines considered not to be related to aniline; no reports of spleen tumours |

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet

### *Summary*

| | Value | Study | Safety factor |
|---|---|---|---|
| ADI | 0–0.02 mg/kg bw | Human volunteer | 10 |
| ARfD | 0.02 mg/kg bw | Human volunteer | 10 |

## RESIDUE AND ANALTYICAL ASPECTS

The insecticide buprofezin was first evaluated by the JMPR in 1991. It was evaluated under the Periodic Review Programme in 2008 when an ADI of 0–0.009 mg/kg bw and an ARfD of 0.5 mg/kg bw were established. Numerous residue reviews have been completed since then; the last was done in 2016. The residue definition for compliance with the MRL and dietary risk assessment for plant and animal commodities is buprofezin. The residue is not fat soluble.

Buprofezin was scheduled at the Fiftieth Session of the CCPR for the evaluation of additional uses by the 2019 JMPR. Residue data on analytical methods, storage stability (aniline), supervised trials (tree nuts), and processed commodities (citrus, grape, apple, olive, tomato (aniline only)) were submitted to the present Meeting.

The buprofezin metabolites BF-9, BF-11, BF-12, BF-25, and BF-26 are not included in the residue definitions and, as such, results for those compounds are not further discussed.

Aniline is a breakdown product of buprofezin. However, aniline is not specific to buprofezin breakdown and exposure may come from many sources. Nevertheless, the Meeting evaluated information to assess the dietary risk from exposure to aniline coming from buprofezin.

### *Methods of analysis*

New information on analytical methods was provided to the Meeting for analysis of buprofezin residues in pecans as well as raw and processed orange, grape, apple, olive, and tomato commodities.

Method 52004A003 was used for the analysis of buprofezin in pecan nutmeats. Residues are extracted using acetonitrile and determined by LC-MS/MS. The Meeting concluded, based on similarity with other methods already deemed acceptable by the JMPR and on mean concurrent recovery (90% at

0.01 mg/kg and 93% at 0.1 mg/kg), that the method is suitable for the analysis of buprofezin in pecan nutmeats, with a validated LOQ of 0.01 mg/kg.

Methods used in the processing studies were LMS0022, GE-04, and NIHON/GLP/0801-1. Extraction solvents were dioxane:HCl for LMS0022, acetonitrile for GE-04, and acetonitrile, acetonitrile:water, or hexane/HCl (citrus oil only) for NIHON/GLP/0801-1. For all methods, residues were determined by LC-MS/MS. The methods were validated for analysis of buprofezin in all matrices tested to an LOQ of 0.01 mg/kg, except Method GE-04 for orange wet pomace (0.5 mg/kg) and orange oil (1 mg/kg).

The methods described for the analysis of aniline were based on the same principles. Concurrent recoveries demonstrated that the methods were suitable for the analysis of aniline in processed apple, grape, olive, and tomato commodities.

### *Stability of residues in stored samples*

The 2009 Meeting concluded that buprofezin was stable for up to 28 months in almond nutmeat and 2.5 months in almond hulls. In residue trials evaluated by the 2009 Meeting, samples of almond nutmeats and hulls were stored frozen for up to 11 months. In studies submitted to the current Meeting, samples of pecans were stored for up to 2.8 months. The Meeting noted that almond hulls are a dry, fibrous commodity and that buprofezin was shown to be stable for at least 28 months in cereal straws. Based on the available storage stability data from almond nutmeats and cereal straws, the Meeting considered the residues in the stored analytical samples of almond and pecan nutmeat and almond hulls to be stable for the storage period incurred during the residue trials.

Residues of aniline were shown to be stable for at least 7 months in apple and grape processed commodities and at least 9 months in olive commodities.

### *Residues in supervised residue trials on crops*

The Meeting received supervised residue trials for application of buprofezin to almonds and pecans.

#### *Tree nuts*

The critical GAP is from the USA for tree nuts and consists of a single, broadcast application at 2.24 kg ai/ha and a PHI of 60 days.

In trials in almond approximating the US GAP, residues in nutmeats were: < 0.05 (6) mg/kg.

In trials in pecan approximating the US GAP, residues in nutmeats were: < 0.05 (5) mg/kg.

Noting that the GAP is for the tree nut group and that almonds and pecans are representative commodities, the Meeting estimated a maximum residue level of 0.05(*) mg/kg, an STMR of 0.05 mg/kg, and an HR of 0.05 mg/kg for residues of buprofezin in the group of tree nuts. The Meeting withdrew its previous recommendation of 0.05(*) mg/kg for almond.

### *Animal feeds*

#### *Almond hulls*

The critical GAP is from the registration on tree nuts in the USA and consists of a single, broadcast application at 2.24 kg ai/ha and a PHI of 60 days.

In trials approximating the US GAP, residues in almond hulls were (n = 7): 0.06, 0.08, 0.15, 0.22 (2), 0.51, and 1.5 mg/kg.

The Meeting estimated a maximum residue level of 3 mg/kg and a median residue of 0.22 mg/kg for buprofezin in almond hulls. This replaced the previous recommendation of 2 mg/kg.

### *Residues in processed commodities*

Processing factors based on data reviewed by the 2008, 2009, and the 2019 Meetings are summarized

below, as well as estimates of maximum residue levels, STMR-P and HR-P, as needed. The Meeting decided to extrapolate the processing factors from orange to citrus fruits.

Table 1 Summary of processing factors, maximum residue levels, STMRs and HRs for buprofezin. Values are from 2019 JMPR unless otherwise indicated

| Crop | Commodity | Processing factors | | Residue, mg/kg | | |
|---|---|---|---|---|---|---|
| | | Individual values | Best estimate | Max. residue level | Median/ STMR/ STMR-P | Highest residue/ HR/ HR-P |
| Orange | Whole fruit | -- | -- | 1 | 0.23 (median) | 0.46 (highest residue) |
| | Flesh | < 0.015, < 0.022, 0.054, 0.066, 0.093, 0.21, 0.23, 0.25, 0.38, 0.40 | 0.17 | -- | 0.039 | 0.078 |
| | Peel (fresh) | 1.1, 1.4, 2.0, 2.3, 2.4, 2.8, 3.0, 3.3, 3.4, 4.1, 4.3, 4.8 | 2.9 | -- | 0.67 | 1.3 |
| | Dried pulp | 1.1, 1.4, 2.4, 2.7 (3), 2.8, 2.9, 4.1, 4.5[a], 4.6, 5.1, 6.0[a], 16 | 4.2 | 5 | 0.97 | 1.9 |
| | Juice (2008=pasteurised; 2019=boiled 15 min.) | 0.06, 0.07, 0.13, 0.24, 0.31, 0.31, 0.56, 0.56[a], 0.58[a], 0.60, 0.63, 0.92, 1.0, 1.3 | 0.52 | -- | 0.12 | -- |
| | Marmalade | 0.14, 0.17, 0.44, 0.88, 0.94, 0.99, 1.1, 1.4, 2.1, 2.6 | 1.1 | -- | 0.25 | -- |
| | Oil | 0.88, 2.2, 2.5, 4.2, 5.6, 6.4, 6.9, 8.1, 8.4, 8.9 | 5.4 | 6 | 1.2 | -- |
| Apple | Whole fruit | -- | -- | 3 | 0.28 | 0.99 |
| | Dried | 0.43, 0.77 | 0.60 | -- | 0.17 | 0.59 |
| | Canned | < 0.055, < 0.063 | < 0.055 | -- | 0.015 | -- |
| | Puree | < 0.055, 0.069 | 0.069 | -- | 0.019 | -- |
| | Jelly | < 0.055, < 0.063 | < 0.055 | -- | 0.015 | -- |
| | Juice (raw) | 0.56[b], 0.58[b] | 0.57 | -- | 0.16 | -- |
| | Pomace (wet) | 1.9[b], 2.1[b] | 2.0 | -- | 0.56 | -- |
| Grape | Berry | -- | -- | 1 | 0.17 | 0.74 |
| | Raisins | 0.20, 0.62, 1.0[a], 1.1, 1.5[b], 1.7[a], 1.9, 2.0[b], 2.4[b], 3.4[b] | 1.6 | 2 | 0.27 | 1.2 |
| | Juice (pasteurised) | < 0.037, 0.068, 0.14[b], < 0.24, 0.31[a], 0.35[a], 0.53[b], 0.63[b], 0.64[b], 0.75 | 0.43 | -- | 0.073 | -- |
| | Wine | 0.16, 0.39, 2.0, 5.1, 0.51[a], 0.52[a], 0.56[a], 0.68[b], 0.69[a], 0.78[a], 1.2[b], 1.4[b] | 1.2 | -- | 0.2 | -- |
| Olive | Whole fruit | -- | -- | 5 | 1.125 | 1.7 |
| | Canned (pickled, fermented) | 0.57, 0.63, 0.85 | 0.68 | -- | 0.76 | 1.2 |
| | Oil (crude) | 0.90, 3.1[b], 3.3, 3.6, 4.1 | 3.5 [c] | 20 | 3.9 | -- |

[a] from JMPR 2008,

[b] from JMPR 2009

[c] Best estimate calculated without the value of 0.9 based on the log KOW of 4.9 at pH 7, which suggests a high fat solubility.

The Meeting decided to extrapolate the processing factors from orange to citrus fruits.

For citrus, dried pulp, the Meeting estimated a maximum residue level of 5 mg/kg to replace the previous recommendation (2 mg/kg), a median residue of 0.97 mg/kg and a highest residue of 1.9 mg/kg

For citrus oil, the Meeting estimated a maximum residue level of 6 mg/kg and an STMR-P of 1.2 mg/kg.

For processed apple and grape commodities, the Meeting confirmed previous recommendations.

For olive oil, raw the Meeting estimated a maximum residue level of 20 mg/kg and an STMR-P of 3.9 mg/kg.

The Meeting evaluated residues of aniline in processed commodities of orange, apple, grape, and olive. In raw and processed commodities of apple, grape, and olive, residues of aniline were either not detected or were <LOQ; therefore, the Meeting decided that those commodities did not contribute significantly to the dietary exposure to aniline from the use of buprofezin. In the orange study, a quantifiable residue of aniline was observed in one sample of orange as well as in peel, juice, marmalade, and oil. The Meeting used the ratio of aniline to buprofezin in whole fruit from that study (0.00093) to convert the STMR and HR for buprofezin in citrus (0.23 and 0.46, respectively (2008 JMPR)) to an aniline-equivalent STMR (0.00021 mg/kg) and HR (0.00043 mg/kg). The Meeting used the aniline-equivalent STMR and HR and the processing factors for aniline in orange (Table 2) to estimate STMR-Ps and HR-Ps for aniline in orange. The Meeting agreed to extrapolate to the group of citrus fruits. As aniline exposure may come from many sources and is not unique to buprofezin, the Meeting did not estimate maximum residue levels for aniline.

Table 2 Summary of processing factors and estimated residues of aniline in raw and processed citrus commodities

| Commodity | Processing factors | Best estimate processing factor | STMR-P, mg/kg | HR-P, mg/kg |
|---|---|---|---|---|
| Whole fruit | -- | -- | 0.00021 (STMR) | 0.00043 (HR) |
| Flesh | n.c., < 0.77 | 0.77 | 0.00016 | 0.00033 |
| Peel (fresh) | > 1, 1.77 | 1.77 | 0.00037 | 0.00076 |
| Dried pulp | n.c., < 0.77 | 0.77 | 0.00016 | -- |
| Juice | n.c., 0.85 | 0.85 | 0.00018 | -- |
| Marmalade | n.c., 2.3 | 2.3 | 0.00048 | -- |
| Oil | > 1.3, 10 | 10 | 0.0021 | -- |

n.c. – not calculable

### *Residues in animal commodities*

The Meeting estimated dietary burdens for livestock based on residues in apple pomace, citrus dried pulp, almond hulls, and soya bean seed. The dietary burdens were estimated using the 2018 OECD Feed diets listed in Appendix XIV Electronic attachments to the 2016 Edition of the FAO manual[8]. The burdens are summarized below.

Table 3 Summary of livestock dietary burdens, as ppm of dry matter, for buprofezin

| | Canada and USA | | European Union | | Australia | | Japan | |
|---|---|---|---|---|---|---|---|---|
| Livestock | Max. | Mean | Max. | Mean | Max. | Mean | Max. | Mean |
| **Beef cattle** | 0.11 | 0.11 | 0.28 | 0.28 | 0.41 [a] | 0.41 [c] | 0.002 | 0.002 |
| **Dairy cattle** | 0.17 | 0.17 | 0.25 | 0.25 | 0.38 [b] | 0.38 [d] | 0.001 | 0.001 |
| **Broiler chickens** | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | -- | -- |

[8] http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmpr/jmpr-docs/en/

| | Canada and USA | | European Union | | Australia | | Japan | |
|---|---|---|---|---|---|---|---|---|
| Livestock | Max. | Mean | Max. | Mean | Max. | Mean | Max. | Mean |
| **Layer hens** | 0.002 [e] | 0.002 [f] | 0.002 | 0.002 | 0.002 | 0.002 | -- | -- |

[a] Highest maximum dietary burden for beef or dairy cattle; suitable for estimating the maximum residue levels for mammalian meat, fat, and offal.

[b] Highest maximum dietary burden for dairy cattle; suitable for estimating the maximum residue levels for milk.

[c] Highest mean dietary burden for beef or dairy cattle; suitable for estimating STMRs for mammalian meat, fat, and offal.

[d] Highest mean dietary burden for dairy cattle; suitable for estimating the STMR for milk.

[e] Highest maximum dietary burden for broiler chickens or laying hens; suitable for estimating the maximum residue levels for poultry meat, fat, offal, and eggs.

[f] Highest mean dietary burden for laying hens; suitable for estimating the STMRs for poultry meat, fat, offal, and eggs.

In the lactating cattle feeding study conducted at 5 and 15 ppm buprofezin in dry feed, residues of buprofezin were not detected in any tissues or in milk. Based on the dietary burdens of 0.41 ppm for beef cattle, 0.38 ppm for dairy cattle, and 0.002 ppm for poultry, the Meeting confirmed its previous recommendations. Noting that recommendations had not been made previously for residues in mammalian fats or for residues in any poultry commodities, the Meeting decided to make maximum residue level estimates of 0.01(*) mg/kg for those commodities, with STMRs and HRs of 0 mg/kg.

## RECOMMENDATIONS

On the basis of the data obtained from supervised trials, the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI and IESTI assessments.

Definition of the residue for compliance with the MRL and for dietary risk assessment for plant and animal commodities: buprofezin.

The residue is not fat-soluble.

## DIETARY RISK ASSESSMENT

### *Long-term dietary exposure*

The ADI for buprofezin is 0–0.009 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for buprofezin were estimated for the 17 GEMS/Food Consumption Cluster Diets using the STMR or STMR-P values estimated by the JMPR. The results are shown in Annex 3 of the 2019 JMPR Report.

The IEDIs ranged from 4–40% of the maximum ADI. The Meeting concluded that long-term dietary exposure to residues of buprofezin from uses considered by the JMPR is unlikely to present a public health concern.

### *Acute dietary exposure*

The ARfD for buprofezin is 0.5 mg/kg bw. The International Estimate of Short-Term Intakes (IESTIs) for buprofezin were calculated for the food commodities and their processed commodities for which HRs/HR-Ps or STMRs/STMR-Ps were estimated by the present Meeting and for which consumption data were available. The results are shown in Annex 4 of the 2019 JMPR Report.

The IESTIs were up to 5% for the general population and up to 10% for children of the ARfD. The Meeting concluded that acute dietary exposure to residues of buprofezin from uses considered by the present Meeting is unlikely to present a public health concern.

### *Aniline*

Aniline is a breakdown product of *inter alia* buprofezin. The current Meeting established a maximum ADI and ARfD for aniline, both at 0.02 mg/kg bw. Information available to the Meeting indicated that the dietary exposure to aniline via buprofezin is minor compared to the estimated dietary exposure to buprofezin itself.

Noting that the ADI for buprofezin is lower than that of aniline, the Meeting concluded that the long-term dietary risk assessment for buprofezin adequately addresses long-term dietary risk to residues of aniline from the use of buprofezin.

For acute dietary exposure, the Meeting estimated residues in commodities from crops evaluated by the Meeting. The estimated acute dietary risk to residues of aniline coming from buprofezin was 0% of the aniline ARfD for both the general population and for children.

Given the multiple sources of aniline, the Meeting recommended that FAO/WHO evaluate aniline as an environmental contaminant.