# EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF QUIZALOFOP-ETHYL

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DRAFT

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## PREFACE

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code 25249.5 *et seq.*) requires that the Governor cause to be published a list of those chemicals "known to the state" to cause cancer or reproductive toxicity. The Act specifies that "a chemical is known to the state to cause cancer or reproductive toxicity … if in the opinion of the state's qualified experts the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity." The lead agency for implementing Proposition 65 is the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. The "state's qualified experts" regarding findings of reproductive toxicity are identified as the members of the Developmental and Reproductive Toxicant (DART) Identification Committee of OEHHA's Science Advisory Board (Title 22, California Code of Regulations, Section 12301) (22 CCR 12301).

Quizalofop-ethyl was identified as a candidate for consideration under the "authoritative bodies" provision of Proposition 65. Subsequent to publication of a notice of intent to list this chemical, it was determined that the data used by the authoritative body did not meet the criteria specified in 22 CCR 12306(g). Pursuant to 22 CCR 12306(i), quizalofop-ethyl has been referred to the DART Identification Committee. This draft document provides the DART Identification Committee with information relevant to the reproductive toxicity of this chemical. While this hazard identification document does not provide dose-response evaluation, exposure assessment or determination of allowable or safe exposure levels, the document does provide information which may be useful in such appraisals.

A public meeting of the Committee will be held on December 13, 1999, in Sacramento, California. Following discussion and Committee deliberation, the Committee will determine whether quizalofop-ethyl "has been clearly shown by scientifically valid testing according to generally accepted principles" to cause reproductive toxicity.

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## A. ABSTRACT

Seven studies investigating the potential for quizalofop-ethyl to cause reproductive or developmental toxicity were reviewed. Two studies, one in rats and one in rabbits, investigated developmental toxicity, while five chronic or subchronic feeding studies provided information on effects on reproductive organs. The rat developmental study included a reproductive component for animals exposed in utero to quizalofop-ethyl, but no other data on functional aspects of reproduction were available.

The studies of the potential effects of quizalofop-ethyl on development were conducted in rabbits and rats. In both studies, quizalofop-ethyl was administered to pregnant females during the period of organogenesis for the species in question. In the rabbit study the highest dose tested (60 mg/kg/day) induced mild toxicity in the dams, but resulted in no apparent treatment-related adverse effects in the fetuses. The rat study included both an evaluation of fetal effects at the end of the gestational period and postnatal evaluation of young that were delivered and suckled by their dams. There was a statistically significant decrease in the number of fetuses alive at the time of sacrifice of the dams on day 21 of gestation in the high dose group receiving 300 mg/kg/day quizalofop-ethyl, and a significant increase in the number of animals with retained placenta in the same group. Postnatal bodyweight in both male and female pups in the 300 mg/kg/day group was significantly lower than control values both pre and post-weaning, and food intake by these animals was also significantly lower than control values. Uterine weights in offspring assessed at age 8 weeks were significantly lower in offspring of 300 mg/kg/day dams than in offspring of controls. There were no apparent effects on developmental landmarks such as incisor budding, hair eruption, descent of testicles or vaginal opening. Assessment of various behavioral indices also revealed no significant differences between treated and control animals. Breeding of male and female offspring at age 10 weeks did not show any differences between control and treated animals in reproductive parameters or in fetal development. Body weight gain and food intake was significantly lower in the 100 and 300 mg/kg/day groups at various points during gestation and lactation.

Potential effects of quizalofop-ethyl on female and male reproductive organs were assessed in two studies in dogs, two studies in rats and one study in mice. There were no apparent pathological effects on ovaries or uterus in either of the dog studies. Both studies were of parallel design except for duration of exposure. Ovarian weights in treated animals varied from control values in both studies, but there was no apparent dose-response relationship and the effects were not reported to be statistically significant. A histopathological finding of testicular atrophy occurred in two males in the first study, and provided the basis for the identification of reproductive toxicity under the U.S. Environmental Protection Agency's Toxic Release Inventory (TRI) process. The severity of the effect was such that spermatogenesis was not impaired, and effects on several other organs and tissues were also noted at this dose level. No testicular atrophy was observed in the second dog study.

Two studies in Sprague-Dawley rats did not show any clear evidence of effects on female reproductive organs. One of those studies demonstrated a high incidence of testicular atrophy at the end of the 13 week treatment period in animals receiving 1280 ppm

quizalofop-ethyl in diet. Testicular atrophy at this level of exposure was also apparent after a 6 week recovery period. Food intake over the treatment period was significantly lower in these animals than in controls, and concurrent manifestations of toxicity included effects on liver and blood. The other study in Sprague-Dawley rats exposed to lower concentrations of quizalofop-ethyl for a much longer period, up to 400 ppm for 104 weeks, did not show any evidence of testicular atrophy.

The only study in mice reviewed showed significantly increased ovarian weights at all dose levels tested (2, 10, 80 and 320 ppm), but no other clear evidence of effect on the ovaries or uterus. However, the study did show evidence of effect on the testes, with bilateral testicular atrophy being reported after exposure for 78 weeks to concentrations of 80 or 320 ppm quizalofop-ethyl in diet. The effect was more pronounced at the higher concentration.

In addition to reports of effects on testes and ovaries, quizalofop-ethyl has been repeatedly shown to affect liver. There are also some indications of effects on kidney, adrenals, thyroid, thymus and blood, but the reports of these effects are less consistent. In studies where developmental and/or reproductive effects were assessed, effects on bodyweight, food intake and organ weights and condition occurred at several levels of exposure.

## B. INTRODUCTION

### B.1 Chemical structure and physical properties

Quizalofop-ethyl [(2-(4-((6-chloro-2-quinoxalinyl)oxy)phenoxy)-ethyl ester] (CAS No. 76578-14-8) is a white crystaline powder with the chemical formula $C_{19}H_{17}ClN_2O_4$ and molecular weight 372.81. It is only slightly soluble in water (Nippon Experimental Medical Research Institute, 1983a).

The chemical structure of quizalofop-ethyl is shown in Figure B.4.1, along with the chemical structure of two of its primary metabolites.

### B.2 Regulatory History

Quizalofop-ethyl was formally identified by the U.S. Environmental Protection Agency (U.S. EPA) as causing reproductive toxicity in the course of implementation of the Toxic Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA)). Quizalofop-ethyl was considered for listing under Proposition 65 because of this formal identification by an authoritative body. Subsequent to publication of a notice of intent to list the chemical, it was determined that the relevant scientific criteria specified in Title 22, California Code of Regulations, Section 12306(g) (22 CCR 12306(g)) had not been met. Accordingly, as required by 22 CCR 12306(i), the chemical has been referred to the State's Qualified Experts so that they can render an opinion as to whether the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. This document reviews of all the available data on the reproductive and developmental toxicity of quizalofop-ethyl, including studies not cited by U.S. EPA in under the TRI process.

Quizalofop-ethyl is not listed under Proposition 65 as a chemical known to cause cancer. It is classified by U.S. EPA as Class D: not classifiable as to human carcinogenicity (U.S. EPA, 1999 – IRIS). This classification is based on no human data and inadequate animal data. It has not been reviewed by the International Agency for Research on Cancer.

Quizalofop-ethyl is a phenoxypropionic ester. 2,4-DB (4-(2,4-dichlorophenoxy)butanoic acid), another chemical in this class of compounds, has been identified under Proposition 65 as causing developmental and male reproductive toxicity.

### B.3 California Use and Exposure Information

Quizalofop-ethyl was formerly used as an herbicide for broadleaf crops. It has not been registered for use as a pesticide in California since 1993.

### B.4 Pharmacokinetics

Information on the pharmacokinetics of quizalofop-ethyl is available from five studies in rats. In general, quizalofop-ethyl is absorbed to a considerable extent by the oral route. Much of what is absorbed is returned to the gastrointestinal tract in bile. Peak blood concentrations occur six to nine hours after exposure, and decline with a half time of

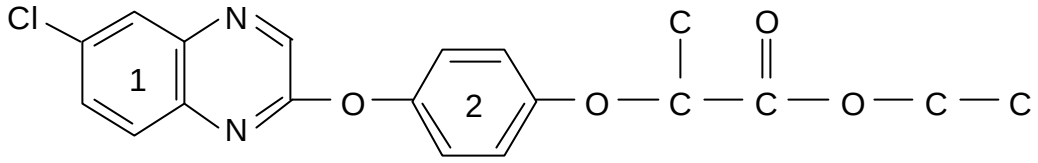
around 20 to 30 hours. Quizalofop-ethyl is metabolized to a number of products, and distributed to most if not all tissues. The main metabolite found in tissues is quizalofop acid (see Figure B.4.1). Generally, most quizalofop-ethyl and its metabolites are excreted in feces. However, there are consistent sex differences in excretion: females excrete more in urine than do males. In females, at lower exposure levels, the amounts excreted in feces and urine are similar. Following oral treatment, some unchanged quizalofop-ethyl is excreted in feces, although the majority is in the form of metabolites, predominantly quizalofop acid. In urine, no unchanged quizalofop-ethyl is found, and the predominant metabolites are quizalofop acid and 2-(4-hydroxyphenoxy)propionic acid (PPA) (see Figure B.4.1).

## B.4.1. Absorption

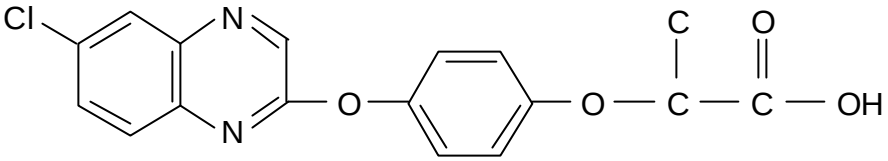
No direct estimates of the extent of absorption from oral exposure were located. Absorption can be inferred from a number of studies where quizalofop-ethyl was found in blood, various tissues, and urine following oral exposure.

Absorption was examined in Sprague-Dawley rats given $^{14}$C-quizalofop-ethyl (quinoxaline labeled: see Figure B.4.1) once orally at 1.5 mg/kg. Radiolabel was found in urine, liver, and carcass. Additionally, in animals with cannulated bile ducts, about half of the label was recovered in bile within 48 hours (Nissan Chemical Industries, Ltd., 1983a). In a similar study, rats were treated with labeled quizalofop-ethyl for 28 days at 1.5 mg/kg/day. Most tissues were labeled (Nissan Chemical Industries, Ltd., 1983b). In a subsequent study, $^{14}$C-quizalofop-ethyl (quinoxaline or phenyl labeled: see Figure B.4.1) was administered once orally to Sprague-Dawley rats at 160 mg/kg. A number of metabolites were detected in urine (Nissan Chemical Industries, Ltd., 1985a). In another study by the same group, rats were pretreated with unlabeled quizalofop-ethyl for 14 days at 1.5 mg/kg/day followed by a single administration of $^{14}$C-quizalofop-ethyl (phenyl labeled: see Figure B.4.1). Again, blood, urine, and most tissues were labeled.

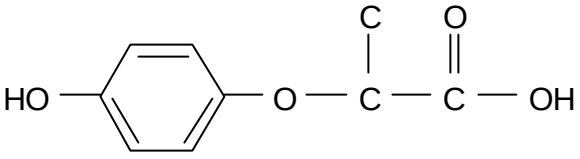
Figure B.4.1. Structure of quizalofop-ethyl and two metabolites




A. Quizalofop-ethyl
1. Location of 14-C label in quinoxaline group
2. Location of 14-C label in phenyl group




B. Quizalofop acid




C. 2-(4-hydroxyphenoxy)propionic acid (PPA)

## B.4.2 Distribution

Quizalofop-ethyl and/or its metabolites are widely distributed following administration to rats. All tissues tested have been found to contain quizalofop-ethyl and/or its metabolites. Peak plasma or blood concentrations occur 6 to 9 hours after oral dosing, with a decay half life of about 20 to 30 hours. A large fraction of quizalofop-ethyl metabolites are excreted in the bile: this is the case whether dosing is oral or by intravenous injection. Distribution was examined in Sprague-Dawley rats given $^{14}$C-quizalofop-ethyl (quinoxaline labeled: see Figure B.4.1) once orally at 1.5 mg/kg. A mean peak plasma concentration of 9.85 µg equivalent/ml occurred six hours after dosing. Concentrations declined with a half-life of 30.9 hours. After 168 hours, plasma concentrations had declined to 0.27 µg equivalent/ml. In rats with cannulated bile ducts, during 48 hours 52.0% and 49.1% of the label was recovered in bile in males and females, respectively. Label was found in liver, kidneys, thyroid and fat. Label in these tissues was lower at all time points than in the plasma, with the exception of fat at 168 hours (Nissan Chemical Industries, Ltd., 1983a).

Table B.4.2.1. Blood and Tissue Concentrations of Radiolabel in Male Rats Treated with $^{14}$C-Quizalofop-Ethyl at 1.5 mg/kg/d for 28 Days (Nissan Chemical Industries, Ltd., 1983b).

| Tissue | Blood | liver | kidney | muscle | fat |
|---|---|---|---|---|---|
| dosing period (days) | | | | | |
| 3 | 5.00 ± 0.58 | 3.19 ± 0.53 | 3.33 ± 0.70 | 0.61 ± 0.14 | 1.35 ± 0.18 |
| 7 | 5.97 ± 0.68 | 4.58 ± 0.40 | 4.20 ± 0.62 | 0.68 ± 0.09 | 1.49 ± 0.16 |
| 14 | 3.80 ± 1.83 | 3.39 ± 1.34 | 3.63 ± 1.34 | 0.48 ± 0.28 | 1.30 ± 0.36 |
| 21 | 2.73 ± 0.40 | 2.63 ±+ 0.42 | 2.36 ± 0.30 | 0.30 ± 0.05 | 1.18 ± 0.07 |
| 28 | 3.33 ± 0.98 | 2.55 ± 0.31 | 3.46 ± 0.54 | 0.38 ± 0.12 | 1.40 ± 0.36 |
| withdrawal period | | | | | |
| 28 + 2 | 1.33 ± 0.18 | 1.20 ± 0.17 | 1.52 ± 0.41 | 0.15 ± 0.00 | 0.97 ± 0.21 |
| 28 + 4 | 0.56 ± 0.32 | 0.47 ± 0.25 | 0.59 ± 0.37 | 0.07 ± 0.04 | 1.26 ± 0.27 |
| 28 + 6 | 0.54 ± 0.36 | 0.34 ± 0.21 | 0.43 ± 0.35 | 0.08 ± 0.04 | 1.07 ± 0.20 |
| 28 + 8 | 0.20 ± 0.10 | 0.13 ± 0.06 | 0.12 ± 0.07 | 0.03 ± 0.02 | 0.96 ± 0.25 |

*Notes: Mean ± S.D. mg quizalofop-ethyl equivalents/g or ml. N = 3/treatment group.*

In a similar study, rats were treated with labeled quizalofop-ethyl for 28 days at 1.5 mg/kg/day. Peak concentrations of label in blood, liver, kidneys, muscle, and fat were found on the seventh day of treatment, but were somewhat lower during the remainder of treatment. After the end of treatment, blood and tissue concentrations declined rapidly, except for fat, which declined relatively slowly (see Table B.4.2.1).

Whole body autoradiography found radioactivity in the gastro-intestinal and urinary tracts, liver, blood, skin, fur, muscle, fat, some endocrine and secretory glands, connective tissue, and to a lesser extent some parts of the reproductive system (Nissan Chemical Industries, Ltd., 1983b).

Distribution was examined in Sprague-Dawley rats using intravenous injection with $^{14}$C-quizalofop-ethyl (phenyl labeled: see Figure B.4.1) once at 10 mg/kg. Distribution of radiolabel was tested at 0, 1, 3, 9, 24, 72, 120 and 168 hours after dosing. Peak concentrations were found in plasma, whole blood, liver, kidney, and brain immediately after dosing (0 hours). Peak concentrations were found in testes and white fat 3 hours after dosing (Nissan Chemical Industries, Ltd., 1985b).

Table B.4.2.2. Tissue Concentrations of Radiolabel from Rats Treated with Unlabeled Quizalofop-Ethyl for 14 days at 1.5 mg/kg/d, Followed by $^{14}$C -Quizalofop-Ethyl at 1.5 mg/kg (Nissan Chemical Industries, Ltd., 1985c).

| Sex | Males | | Females | |
|---|---|---|---|---|
| time after last treatment | 24 hr | 168 hr | 24 hr | 168 hr |
| tissues | | | | |
| whole blood | 1.85 ± 0.14 | 0.01 ± 0.01 | 1.72 ± 0.18 | 0.02 ± 0.00 |
| plasma | 3.11 ± 0.26 | 0.02 ± 0.01 | 2.95 ± 0.27 | 0.03 ± 0.00 |
| liver | 1.08 ± 0.04 | 0.01 ± 0.00 | 0.96 ± 0.08 | 0.01 ± 0.00 |
| kidney | 1.28 ± 0.07 | 0.01 ± 0.00 | 1.17 ± 0.12 | 0.02 ± 0.00 |
| heart | 0.48 ± 0.05 | <0.01 | 0.47 ± 0.05 | <0.01 |
| lung | 0.60 ± 0.05 | <0.01 | 0.60 ± 0.09 | <0.01 |
| brain | 0.04 ± 0.00 | <0.01 | 0.03 ± 0.00 | <0.01 |
| pancreas | 0.35 ± 0.03 | <0.01 | 0.33 ± 0.03 | <0.01 |
| spleen | 0.22 ± 0.02 | <0.01 | 0.21 ± 0.02 | <0.01 |
| eye | 0.13 ± 0.01 | <0.01 | 0.10 ± 0.01 | <0.01 |
| testes | 0.30 ± 0.03 | <0.01 | - | - |
| epididymis | 0.47 ± 0.03 | 0.01 ± 0.01 | - | - |
| ovary | - | - | 0.48 ± 0.04 | <0.01 |
| uterus | - | - | 0.67 ± 0.08 | <0.01 |
| fat | 0.18 ± 0.02 | 0.02 ± 0.01 | 0.24 ± 0.04 | 0.01 ± 0.00 |

*Note: Mean ± S.E. mg quizalofop-ethyl equivalent/g. N = 5/group.*

Distribution was examined in Sprague-Dawley rats treated orally with unlabeled quizalofop-ethyl for 14 days at 1.5 mg/kg/d, and then treated with $^{14}$C-quizalofop-ethyl (phenyl labeled: see Figure B.4.1) at 1.5 mg/kg. Blood samples were taken at 0.25, 1, 3, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 hours after treatment with $^{14}$C-quizalofop-ethyl. Peak blood concentrations of label were found 9 hours after treatment in both

males and females. Biological half life was about 20 hours. After 24 hours, label was found in all tissues tested, including testes and ovaries (see Table B.4.2.2). Concentrations of label in tissues from males and females were similar (Nissan Chemical Industries, Ltd., 1985c).

## B.4.3 Metabolism

Metabolites of quizalofop-ethyl have been found in plasma, tissues, urine, feces, and bile. There appear to be two major metabolites plus a large number of other metabolites and conjugates of metabolites. One prominent metabolite is the ethyl ester hydrolysis product quizalofop acid. Another prominent metabolite is the ether hydrolysis product of quizalofop acid, 2-(4-hydroxyphenoxy)propionic acid (PPA) (see Figure B.4.1). There is evidence that there may be quantitative differences in the metabolites produced by male rats versus female rats.

Metabolites of quizalofop-ethyl were studied in Sprague-Dawley rats given $^{14}C$-quizalofop-ethyl (quinoxaline labeled: see Figure B.4.1) once orally at 1.5 mg/kg. Metabolites were resolved by thin layer chromatography (TLC) using one of two solvent systems. Except for the parent quizalofop-ethyl, specific identification of metabolites was not conducted. In urine, TLC resolved five metabolites plus material remaining at the origin. Some of the material remaining at the origin was cleaved by B-glucuronidase/sulphatase treatment at pH 5, with the resulting compounds co-migrating with the previously resolved compounds. There were substantial quantitative differences between the amounts of material in the various components in males versus females. No unchanged quizalofop-ethyl was found in the urine. In methanol extracts of feces, TLC results were qualitatively similar to urine (five metabolites plus baseline), although the relative amounts of the different metabolites were different. There was some difference in the relative amounts of metabolites in males versus females. In bile, TLC resolved one metabolite in males and two metabolites in females, plus material remaining at the origin. Some of the material remaining at baseline was cleaved by B-glucuronidase/sulphatase treatment at pH 5. No unchanged quizalofop-ethyl was found (Hawkins et al 1983a).

Metabolites of quizalofop-ethyl were studied in Sprague-Dawley rats given $^{14}C$-quizalofop-ethyl (phenyl labeled: see Figure B.4.1) once by intravenous injection at 10 mg/kg. Metabolites were resolved by TLC using a slightly different solvent system than the ones used above. Migration of metabolites was compared to authentic standards for quizalofop-ethyl, quizalofop acid, 4-(6-chloro-2-quinoxalinyloxy)phenol (CQP), and PPA. Ethyl acetate extracts of urine from males were resolved by TLC into five components plus material remaining at the origin. Three of these co-migrated with PPA, quizalofop acid, and CQP. The most prominent metabolite in urine was PPA (47% of label in sample). Methanol extracts of feces from males were resolved into the same five components plus material remaining at the origin. The most prominent metabolite in feces was quizalofop acid (50% of label in sample). No unchanged quizalofop-ethyl was found in either urine or feces (Nissan Chemical Industries, Ltd., 1985b).

Metabolites of quizalofop-ethyl were studied in Sprague-Dawley rats given $^{14}C$-quizalofop-ethyl (quinoxaline or phenyl labeled: see Figure B.4.1) once orally at 160 mg/kg. Metabolites were resolved by TLC using one of two solvent systems. Migration of metabolites was compared to authentic standards for quizalofop-ethyl, quizalofop acid, CQP, PPA, 6-chloroquinoxalin-2-one (CQO) and dihydroquinoxaline (DHQ). Additionally, gas chromatography-mass spectrometry (GC-MS) was performed on some samples. Metabolites detected using TLC for the phenyl labeled quizalofop-ethyl were similar to those detected in the intravenous study above. Metabolites detected for the quinoxaline labeled quizalofop-ethyl included those metabolites and one additional metabolite. The authors concluded that this additional metabolite contained the quinoxaline group but not the phenyl group. The identification of quizalofop acid and PPA was confirmed by GC-MS. Results from GC-MS also suggested that one of the unknown metabolites was hydroxylated quizalofop acid, and that the unknown metabolite found only with the quinoxaline label was hydroxylated chloroquinoxaline. Additionally, it was found that the major metabolite in plasma, liver, kidney, brain and fat was quizalofop acid (Nissan Chemical Industries, Ltd., 1985a).

Table B.4.3.1. Proportions of Label Found in Rat Tissues Following Exposure to 1.5 mg/kg/d Quizalofop-Ethyl for 14 Days and $^{14}C$-Quizalofop-Ethyl (Phenyl Labeled) Once at 1.5 mg/kg (Nissan Chemical Industries, Ltd., 1985c).

| | males | | | females | | |
|---|---|---|---|---|---|---|
| | plasma | liver | kidney | plasma | liver | kidney |
| organic soluble | 100 | 92.5 | 97.4 | 99.7 | 94.5 | 98.1 |
| quizalofop-ethyl | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| quizalofop acid | 95.5 | 83.6 | 88.8 | 93.9 | 86.5 | 88.3 |
| CQP | 0.2 | 1.0 | 1.2 | 0.2 | 0.7 | 1.0 |
| PPA | 0.2 | 1.9 | 1.2 | 0.1 | 1.5 | 1.7 |
| AM-1 | 0.6 | 0.6 | 0.5 | 0.4 | 0.5 | 0.5 |
| AM-2 | 2.2 | 0.7 | 1.2 | 3.6 | 2.0 | 1.7 |
| origin | 0.2 | 2.0 | 2.8 | 0.2 | 0.7 | 2.9 |
| others | 1.0 | 2.8 | 1.7 | 1.3 | 2.6 | 2.0 |

*Note: Results are from TLC separation of organic soluble extracts, expressed as percent of total label. AM-1 and AM-2 are unknown metabolites. Suggestive evidence indicates that AM-2 may be hydroxylated quizalofop acid.*

Metabolites of quizalofop-ethyl were studied in Sprague-Dawley rats treated orally with unlabeled quizalofop-ethyl for 14 days at 1.5 mg/kg/d, and then treated with $^{14}C$-quizalofop-ethyl (phenyl labeled: see Figure B.4.1) at 1.5 mg/kg. Metabolites were resolved by TLC using one of two solvent systems (as in Nissan Chemical Industries, Ltd., 1985a, above). Metabolites detected using TLC were the same as those identified with the phenyl labeled quizalofop-ethyl in the intravenous and single oral studies above (Nissan Chemical Industries, Ltd., 1985b). As in the single oral exposure study, the

major metabolite found in plasma, liver, and kidney was quizalofop acid. There was no major difference between sexes. In contrast to feces and urine, there were only very small amounts of PPA found in tissues (see Table B.4.3.1) (Nissan Chemical Industries, Ltd., 1985c).

## B.4.4 Excretion

Several studies have examined the excretion of quizalofop-ethyl in rats using $^{14}$C-quizalofop-ethyl labeled in either the quinoxaline or phenyl groups. In general, most quizalofop-ethyl and/or its metabolites are excreted in feces. However, there is a sex difference in excretion, with females excreting relatively more in the urine, and less in feces, than males. In females, at lower exposure levels, the amounts excreted in feces and urine are similar. Label was not found in exhaled air. In urine, all label was found as metabolites, predominantly either PPA or quizalofop acid. In feces, following oral treatment, most label was found as metabolites, predominantly quizalofop acid. Some label in feces was found as unchanged quizalofop-ethyl, especially at a high dose level. When treated by intravenous injection, feces was the major route of excretion, probably resulting from excretion in bile. All label was found in metabolites.

Excretion was studied in Sprague-Dawley rats treated once orally with $^{14}$C-quizalofop-ethyl (quinoxaline labeled: see Figure B.4.1) at 1.5 mg/kg. Over five days, in male rats it was found that 21.0% of label was excreted in the urine, and 74.5% of label was excreted in the feces. In contrast, in female rats, 49.8% was excreted in the urine, and 49.1% in the feces. No label was found in exhaled air. Label in urine consisted entirely of metabolites and conjugates of metabolites: no unchanged quizalofop-ethyl was found. Label in feces consisted mainly of metabolites and conjugates. Over the first two days, small amounts of unchanged quizalofop-ethyl were found in both males and females (7% and 10%, respectively) (Nissan Chemical Industries, Ltd., 1983a).

Excretion was studied in Sprague-Dawley rats treated with $^{14}$C-quizalofop-ethyl (phenyl labeled: see Figure B.4.1) by intravenous injection once at 10 mg/kg. Over seven days, in male rats it was found that 16.5% of label was excreted in the urine, and 70.9% was excreted in the feces. In contrast, in female rats, 38.7% was excreted in the urine, and 51.1% in the feces. Most label was excreted in the first three days. No label was found in exhaled air. Label in urine and feces consisted entirely of metabolites and conjugates of metabolites: no unchanged quizalofop-ethyl was found. In male rats the predominant metabolite in urine was PPA (47.0% of total), whereas in feces it was quizalofop acid (49.6% of total) (Nissan Chemical Industries, Ltd., 1985b).

Excretion was studied in Sprague-Dawley rats treated with $^{14}$C-quizalofop-ethyl (quinoxaline or phenyl labeled: see Figure B.4.1) once orally at 160 mg/kg. Over 2 days, in male rats treated with phenyl labeled compound, it was found that 5.3% of the label was excreted in urine and 73.2% was excreted in feces. In females, 16.5% was excreted in urine and 58.6% in feces. In male rats treated with quinoxaline labeled compound, results were nearly identical to the phenyl labeled compound, with 5.5% excreted in urine and 72.6% in urine. In rats treated with the phenyl labeled compound, all label in urine

was metabolites. In males, the predominant metabolite was PPA (49.4%), whereas in females the predominant metabolite was quizalofop acid (53.4%). If feces, in males 30.7% of label was unchanged quizalofop-ethyl. In females, it was 38.6% of label. In both males and females, quizalofop acid was the main metabolite found in feces (33.6% and 24.7%, respectively). The authors concluded that the unchanged quizalofop-ethyl found in feces had not been absorbed (Nissan Chemical Industries, Ltd., 1985a).

Excretion was studied in Sprague-Dawley rats treated with unlabeled quizalofop-ethyl orally for 14 days at 1.5 mg/kg/d, followed by one treatment with $^{14}$C-quizalofop-ethyl (phenyl labeled: see Figure B.4.1). Over 7 days, in male rats, it was found that 23.1% of the label was excreted in urine and 72.9% was excreted in feces. In females, 49.2% was excreted in urine and 44.9% in feces. No label was found in exhaled air. Most label was excreted in the first three days. All label in urine was metabolites. In males, similar proportions of PPA and quizalofop acid were found (25.2% and 22.3%, respectively). In females, the predominant metabolite was quizalofop acid (73.2%). In feces, some unchanged quizalofop acid was found (4.9% in males, 5.8% in females). The predominant label was in quizalofop acid (42.7% in males, 47.0% in females) (Nissan Chemical Industries, Ltd., 1985c).

## B.5 Non-DART Toxicity

In addition to reports of effects on testes and ovaries, quizalofop-ethyl has been repeatedly shown to affect liver. There are also some indications of effects on kidney, adrenals, thyroid and thymus weights, and on blood parameters such as red corpuscle count and neutrophil number, but the reports of these effects are less consistent. Data on non-DART toxicity occurring in studies where developmental and/or reproductive effects were assessed are included in summaries of individual studies below.

# C. DEVELOPMENTAL AND REPRODUCTIVE TOXICITIES

## C.1. Developmental Toxicity

### *C.1.1. Human Developmental Toxicology Studies*

No studies or reports pertaining to developmental toxic effects of quizalofop-ethyl in humans were identified on the basis of comprehensive computerized literature searches.

### *C.1.2. Animal Developmental Toxicology Studies*

A developmental toxicity study in rabbits and a combined developmental and reproductive toxicity study in rats are available. Neither of these studies was cited by U.S. EPA under TRI.

**Nippon Experimental Medical Research Institute, 1983a**. New Zealand white rabbits were administered quizalofop-ethyl by oral gavage on days 6-18 of gestation. Dose levels of 0 (control), 7, 15, 30 or 60 mg/kg/day were reported to be based on a preliminary experiment. The test material was dissolved in 0.5% CMC (not defined in the study report, assumed to be carboxymethyl cellulose), with the concentration adjusted such that each animal was administered a volume of 5 ml/kg; control animals were administered 5 ml of vehicle only. Animals were bred at approximately seven months of age and, after confirmation of the presence of sperm in a vaginal smear (designated as day 0 of pregnancy), female were randomly assigned to treatment groups. There were 15-18 pregnant females/group.

Daily observations were made of the pregnant females, and body weights were measured on days 0, 6-19, 21, 23, 25, 27 and 29. Animals had *ad libitum* access to food and tap water, and intake of both was measured daily throughout pregnancy. All females were laparotomized on day 29 of gestation. All fetuses were weighed and examined for external malformations. One male and one female fetus that were closest to the end of the right uterine horn from each dam were collected and used for skeletal examinations, and one male and one female fetus that were next closest to the end of the right uterine horn were used for visceral examinations.

Two dams died during gestation, one dam in the control group on day 23 of gestation and one dam in the 30 mg/kg group on day 24 of gestation. Neither death appeared to be treatment-related. Two females in the 30 mg/kg group had partial abortions; one animal aborted two fetuses on day 24, and retained six fetuses, while the other aborted one fetus on day 16 and retained six fetuses. One female in the 15 mg/kg group gave premature birth to six young on day 29 of gestation, and retained one normal fetus and two resorbed embryos in her uterus. Data from these animals are not included in the summary data presented in Table C.1.2.1.

The study report concluded that administration of 60 mg/kg/day resulted in adverse effects on the dams including decreased weight gain and food intake, and reduced thymus and thyroid gland weights, but that there was no adverse effects on the fetuses. It was also concluded that no adverse effects on dams or fetuses resulted from administration of 30 mg/kg/day.

The results of laparotomies are summarized in Table C.1.2.1. The only parameter to differ significantly between controls and any treatment group was the slightly higher proportion of female fetuses in the 30 mg/kg/day group (57.7% compared to 44.4% in the control group). The corresponding difference in proportion of male fetuses was not statistically significant (42.3% in the 30 mg/kg/day group compared to 55.6% in the control group). No significant difference was seen in the proportions of female and male fetuses in the 60 mg/kg/day group compared to controls (53.2% female and 46.8% male fetuses in the 60 mg/kg/day group).

Table C.1.2.1. Observations of Uterine Contents in Rabbits Orally Exposed to Quizalofop-Ethyl on days 6-18 of Gestation. (Nippon Experimental Medical Research Institute, 1983a).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 mg/kg (control) | 7 mg/kg | 15 mg/kg | 30 mg/kg | 60 mg/kg |
| Number of dams | 16 | 18 | 15 | 12 | 15 |
| Number of corpora lutea (mean ± S.D.) | 148 (9.3±1.8) | 174 (9.7±1.7) | 138 (9.2±2.7) | 117 (9.8±1.4) | 155 (10.3±2.0) |
| Number of implantations (mean ± S.D.) | 130 (88%) (8.1±2.2) | 167 (96%) (9.3±2.0) | 130 (94%) (8.7±3.2) | 106 (91%) (8.8±2.0) | 136 (88%) (9.1±2.5) |
| Number of live fetuses (mean ± S.D.) | 117 (90%) (7.3±2.5) | 160 (96%) (8.9±2.0) | 117 (90%) (7.8±3.1) | 104 (98%) (8.7±1.9) | 124 (91%) (8.3±2.8) |
| Number of male fetuses (mean ± S.D.) | 65 (55.6%) (4.3±1.9) | 79 (49.4%) (4.4±2.0) | 59 (50.4%) (3.8±1.9) | 44 (42.3%) (3.7±1.8) | 58 (46.8%) (3.9±1.5) |
| Number of female fetuses (mean ± S.D.) | 52 (44.4%) (3.3±1.5) | 81 (50.6%) (4.5±2.5) | 58 (49.6%) (4.1±1.7) | 60 (57.7%) (5.0±0.8)** | 66 (53.2%) (4.4±2.3) |
| Number of immature fetuses | 6 (5.1%) | 3 (1.9%) | 6 (5.1%) | 3 (2.9) | 5 (4.0%) |
| Number of resorptions | | | | | |
| Implantation trace | 0 | 0 | 0 | 0 | 0 |
| Placental remnant | 3 (2.3%) | 2 (1.2%) | 0 | 1 (0.8%) | 2 (1.5%) |
| Early resorption | 0 | 4 (2.4%) | 1 (0.8%) | 0 | 5 (3.7%) |
| Late resorption | 8 (6.2%) | 1 (0.6%) | 5 (3.8%) | 1 (0.8%) | 5 (3.7%) |
| Macerated fetus | 2 (1.5%) | 0 | 7 (5.4%) | 0 | 0 |
| Malformations | 0 | 0 | 0 | 0 | 0 |
| Fetal body weight (g) | | | | | |
| Male (mean ± S.D.) | 38.65±6.02 | 36.35±6.28 | 38.08±6.92 | 37.65±4.42 | 39.17±8.25 |
| Female (mean ± S.D.) | 36.63±7.37 | 35.46±6.72 | 36.98±6.60 | 37.52±4.14 | 37.86±9.17 |

*** p<0.01 (t-test)*

The results of fetal skeletal examinations are summarized in Table C.1.2.2, and the results of fetal visceral examinations in Table C.1.2.3. Skeletal anomalies noted in the text of the report were vertebral dysplasia, synostosis of the coccygeal vertebrae and sternal stynosis. There were no significant differences in the frequency of appearance of any of these anomalies in the control or any treatment group. Similarly, there were no significant differences between the incidence of visceral malformations among control and treatment groups.

Table C.1.2.2. Results of Fetal Skeletal Examinations in Rabbits Orally Exposed to Quizalofop-Ethyl on days 6-18 of Gestation. (Nippon Experimental Medical Research Institute, 1983a).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 mg/kg (control) | 7 mg/kg | 15 mg/kg | 30 mg/kg | 60 mg/kg |
| Number of dams | 16 | 18 | 15 | 12 | 15 |
| Number of fetuses examined | 62 | 89 | 63 | 57 | 67 |
| Number of dams with malformed fetuses (%) | 2 (12.5) | 3 (16.7) | 2 (13.3) | 1 (8.3) | 0 |
| Number of fetuses with malformations (%) | 2 (3.2) | 4 (4.5) | 3 (4.8) | 1 (1.8) | 0 |
| Number of dams with fetuses showing variations(%) | 14 (87.5) | 18 (100) | 14 (83.3) | 11 (91.7) | 12 (80.0) |
| Number of fetuses with variations (%) | 37 (59.7) | 64 (71.8) | 42 (66.7) | 40 (70.2) | 36 (53.7) |
| Malformations (%) | | | | | |
| Vertebrae dysplasia | 0 | 1 (1.1) | 0 | 0 | 0 |
| Fusion of caudal centra 16-17 | 0 | 1 (1.1) | 0 | 0 | 0 |
| Fusion of sternebrae | 2 (3.2) | 3 (3.4) | 3 (4.8) | 1 (1.8) | 0 |
| Variations (%) | | | | | |
| Excess sternebrae | 1 (1.6) | 0 | 0 | 0 | 0 |
| Thoracic vertebrae 1-13 (normal 1-12) | 1 (1.6) | 1 (1.1) | 0 | 1 (1.8) | 1 (1.5) |
| Lumbar vertebrae 1-7 (normal 1-8) | 28 (45.2) | 45 (50.5) | 27 (42.9) | 31 (54.4) | 21 (31.3) |
| Sacral vertebrae 1-5 (normal 1-4) | 0 | 2 (2.2) | 0 | 0 | 0 |
| Sacral vertebrae 1-3 (normal 1-4) | 2 (3.2) | 2 (2.2) | 3 (4.8) | 0 | 2 (3.0) |
| Cervical rib (right) | 0 | 0 | 0 | 1 (1.8) | 0 |
| Cervical rib (both) | 0 | 0 | 0 | 0 | 1 (1.5) |
| 13th rib 1-13(both) (normal 1-12) | 1 (1.6) | 1 (1.1) | 0 | 1 (1.8) | 1 (1.5) |
| Lumbar rib 1-13(right)[a] | 18 (29.0) | 36 (40.4) | 18 (28.6) | 24 (42.1) | 23 (34.3) |
| Lumbar rib 1-13(right)[b] | 8 (12.9) | 15 (16.9) | 12 (19.0) | 3 (5.3) | 1 (1.5)* |
| Lumbar rib 1-13(right)[c] | 0 | 0 | 2 (3.2) | 0 | 1 (1.5) |
| Lumbar rib 1-13(left)[a] | 17 (27.4) | 36 (40.4) | 19 (30.2) | 23 (40.4) | 21 (31.3) |
| Lumbar rib 1-13(left)[b] | 9 (14.5) | 10 (11.2) | 10 (15.9) | 4 (7.0) | 4 (6.0) |
| Lumbar rib 1-13(left)[c] | 1 (1.6) | 2 (2.2) | 0 | 2 (3.5) | 0 |
| Lumbar rib 1-13(both) | 22 (35.5) | 44 (49.4) | 26 (41.3) | 24 (42.1) | 22 (32.8) |

*[a] Lumbar rib is not less than half of 12th rib [b] Lumbar rib is less than half of 12th rib*
*[c] 13th rib is vestigial * $p<0.05$*

Table C.1.2.3. Results of Fetal Visceral Examinations in Rabbits Orally Exposed to Quizalofop-Ethyl on days 6-18 of Gestation. (Nippon Experimental Medical Research Institute, 1983a).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 mg/kg (control) | 7 mg/kg | 15 mg/kg | 30 mg/kg | 60 mg/kg |
| Number of dams | 15 | 18 | 14 | 12 | 15 |
| Number of fetuses examined | 49 | 68 | 48 | 44 | 52 |
| Number of dams with malformed fetuses (%) | 3 (20) | 3 (16.7) | 0 | 1 (8.3) | 0 |
| Number of fetuses with malformations (%) | 3 (6.1) | 3 (4.4) | 0 | 2 (4.5) | 1 (1.9) |
| Malformations (%) | | | | | |
| Dilation of lateral ventricle | 0 | 1 (1.5) | 0 | 0 | 0 |
| Absence of thymic right lobe | 0 | 1 (1.5) | 0 | 0 | 1 (1.9) |
| Bifid apex of the heart | 2 (4.1) | 1 (1.5) | 0 | 1 (2.3) | 0 |
| Ventricular rotation and hypoplastic left ventricle | 0 | 0 | 0 | 1 (2.3) | 0 |
| Hemopericardium | 0 | 1 (1.5) | 0 | 0 | 0 |
| Hypoplastic aortic valve and pulmonary valve | 1 (2.0) | 0 | 0 | 0 | 0 |

Incidence of skeletal variations did not differ significantly between control and treatment groups, with the single exception of a decreased incidence of right lumbar vertebrae (less than half the length of the 12$^{th}$ rib) in the 60 mg/kg/day group. This difference was not considered treatment-related by the study authors. There was also considered to be no effect on rate of ossification, although partial, mild delay in ossification of the coccygeal vertebrae was noted in the 30 and 60 mg/kg/day groups; there was no significant difference between the average number of ossified coccygeal vertebrae between control and any treatment group.

**Nippon Experimental Medical Research Institute, 1983b**. Pregnant rats of strain Jcl:SD aged 10-12 weeks at the beginning of the experiment were administered quizalofop-ethyl by oral gavage on days 6-15 of gestation, at dose levels of 0 (control), 30, 100 or 300 mg/kg/day. Doses were reportedly based on a preliminary study in which an acute oral $LD_{50}$ of 1,480 mg/kg quizalofop-ethyl in female rats of this strain was established, with one fifth of this dose being selected as the high exposure level in the developmental toxicity study and the lower doses being selected as common increments of that dose. The test material was dissolved in 0.5% CMC (not defined in the study report, assumed to be carboxymethyl cellulose) such that each animal received 2 ml/kg/day of CMC. Vehicle controls received only 2 ml CMC. A positive control group

received 60000 IU of vitamin A in the same volume of CMC, also via oral gavage but on days 8-10 of gestation only. Animals were randomly assigned to treatment groups. Part of each treatment group (or the entire group in the case of the positive controls) was scheduled for sacrifice and laparotomy on day 21 of gestation, while the reminder of each group was allowed to deliver and rear their young. The numbers of animals in each subgroup are shown in Table C.1.2.4. The offspring of the animals in the nursing subgroups were assessed for physical and behavioral development, and for reproductive ability.

Dams were observed daily throughout gestation for death, abortion and general condition. Body weights were recorded on days 0 and 6-21 of gestation, cumulative food intake was measured on day 6 of gestation and daily food intake on days 7-21 of gestation. No information on measurement of water intake was provided in the study report. Weight gain over gestation of pregnant females scheduled for laparotomy is shown in Table C.1.2.5. Mean body weights on each of days 6-16 of gestation were significantly lower than control weights in animals receiving 100 mg/kg quizalofop-ethyl ($p<0.05$ for each day), but the overall reduction in body weight gain over this period, and over the periods of days 0-21 and 6-21 of gestation, were not statistically significant. For animals receiving 300 mg/kg quizalofop-ethyl, mean body weights were reduced on days 15 and 16 of gestation ($p<0.05$). The mean weight gain in this group for days 6-16 was also significantly reduced compared to controls ($p<0.001$), while the reductions in weight gain over the periods of days 0-21 and 6-21 of gestation were not statistically significant.

Table C.1.2.4. Distribution of Pregnant Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation across Treatment Groups. (Nippon Experimental Medical Research Institute, 1983b).

| Treatment Group | Number of dams in laparotomized subgroup | Number of dams in nursing subgroup |
|---|---|---|
| 0 mg/kg (Vehicle Control) | 21 | 14 |
| 30 mg/kg | 21 | 13 |
| 100 mg/kg | 22 | 13 |
| 300 mg/kg | 24 | 14 |
| Positive Control (60000 IU vitamin A) | 20 | 0 |

There were also significant differences in mean daily food intake across the treatment groups, at various timepoints (Table C.1.2.6). In the 30 mg/kg group, mean food intake was increased on day 20 of gestation only ($p<0.05$). In the 100 mg/kg group, significant reductions in mean food intake occurred on days 7 and 8 of gestation ($p<0.01$ and $p<0.001$, respectively). In the 300 mg/kg group, mean food intake was significantly reduced on days 7 ($p<0.05$), 8 ($p<0.001$), 9 ($p<0.001$), 10 ($p<0.05$), 11 ($p<0.01$), 12 ($p<0.01$) and 13 ($p<0.01$), while mean food intake was significantly increased on days 20 and 21 of gestation ($p<0.001$).

Table C.1.2.5. Body Weight Gain over the Gestational Period in Laparotomized Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (Mean Body Weight (g) ± S.E.) | | | | | |
|---|---|---|---|---|---|---|
| Day of Gestation | 0 mg/kg (vehicle control) (n=21) | 30 mg/kg (n=21) | 100 mg/kg (n=22) | 300 mg/kg (n=24) | | 60000 IU Vitamin A (positive control) (n=20) |
| 0 | 271.4±4.23 | 273.3±5.34 | 264.9±2.51 | 273.2±5.04 | | 269.2±3.67 |
| 6 | 294.0±4.30 | 298.6±4.44 | 286.5±3.11 | 295.1±4.75 | | 293.3±3.53 |
| 7 | 297.9±4.48 | 300.8±4.88 | 286.5±2.83* | 293.8±4.51 | | 296.8±3.69 |
| 8 | 300.4±4.34 | 302.3±4.75 | 288.2±3.18* | 291.8±4.57 | | 300.4±3.58 |
| 9 | 303.1±4.51 | 306.2±4.80 | 291.5±2.64* | 294.6±5.09 | | 300.8±4.25 |
| 10 | 308.4±5.12 | 311.3±4.83 | 295.5±2.59* | 297.6±5.10 | | 293.5±4.22* |
| 11 | 313.4±4.63 | 315.2±4.51 | 301.3±2.96* | 301.5±5.05 | | 281.2±4.12*** |
| 12 | 318.6±4.70 | 320.1±4.58 | 305.7±3.18* | 305.0±4.99 | | 275.5±4.28*** |
| 13 | 323.6±4.92 | 324.8±4.49 | 310.4±3.12* | 311.2±4.84 | | 275.9±4.25*** |
| 14 | 329.0±4.95 | 329.1±4.69 | 314.8±3.08* | 317.7±4.23 | | 284.9±4.68*** |
| 15 | 338.2±5.07 | 337.6±4.72 | 323.6±3.43* | 323.6±4.76* | | 292.3±4.94*** |
| 16 | 348.5±5.32 | 348.7±4.84 | 333.9±3.46* | 333.3±4.95* | | 300.2±5.22*** |
| 17 | 362.7±5.59 | 364.1±5.01 | 349.5±3.66 | 347.8±5.04 | | 307.5±5.63*** |
| 18 | 378.4±5.97 | 377.9±5.48 | 366.0±3.57 | 367.4±5.62 | | 312.3±6.89*** |
| 19 | 393.2±6.01 | 393.4±5.61 | 381.0±3.79 | 379.9±5.34 | | 315.4±7.79*** |
| 20 | 409.8±6.55 | 410.7±5.95 | 397.6±4.09 | 398.3±6.24 | | 321.9±9.50*** |
| 21 | 424.9±6.9 | 425.7±6.2 | 412.6±4.5 | 419.1±6.1 | | 328.9±10.9*** |
| Days 0-21 (gain) | 153.4±4.09 | 152.4±5.68 | 147.7±2.84 | 145.9±4.08 | | 59.7±9.48*** |
| Days 6-21 (gain) | 130.9±3.65 | 127.1±4.17 | 126.2±2.44 | 124.0±3.37 | | 35.6±8.92*** |
| Days 6-16 (gain) | 54.5±1.84 | 50.1±1.86 | 47.5±2.19 | 38.2±2.87*** | | 6.9±3.11*** |

** p<0.05 ** p<0.01 *** p<0.001 (Student's t-test)*

Effects on organ weights in treated dams were minimal, with mean absolute liver weight being elevated by 19% ($p<0.001$) and mean absolute pancreas weight being elevated by 16% ($p<0.05$) in the 300 mg/kg group; only the increase in liver weight was considered to be treatment related by the study authors.

It was reported that no remarkable symptoms were observed in any of the treated animals in the laparotomized subgroup, and that none of the dams in the nursing groups manifested any noticeable general symptoms.

Table C.1.2.6. Food Intake over the Gestational Period by Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (Mean Food Intake (g) ± S.E.) | | | | | |
|---|---|---|---|---|---|---|
| Day of Gestation | 0 mg/kg (vehicle control) (n=21) | 30 mg/kg (n=21) | 100 mg/kg (n=22) | 300 mg/kg (n=24) | | 60000 IU Vitamin A (positive control) (n=20) |
| 0 - 6 | 21.7±0.47 | 22.3±0.52 | 21.7±0.58 | 22.0±0.53 | | 21.8±0.57 |
| 7 | 22.7±0.96 | 22.8±0.61 | 19.6±0.55** | 19.5±0.87* | | 22.4±0.92 |
| 8 | 23.7±0.69 | 22.8±0.97 | 19.5±0.69*** | 16.7±1.20*** | | 23.5±1.06 |
| 9 | 24.0±0.76 | 23.7±1.10 | 21.5±0.95 | 18.3±1.30*** | | 17.4±1.09*** |
| 10 | 25.0±0.96 | 23.8±0.79 | 23.3±0.76 | 21.0±1.57* | | 10.2±1.04*** |
| 11 | 26.0±0.77 | 25.0±0.75 | 24.4±0.79 | 22.0±1.16** | | 5.6±1.00*** |
| 12 | 27.1±0.71 | 25.9±0.79 | 25.5±0.49 | 22.3±1.15** | | 8.3±1.22*** |
| 13 | 27.4±0.66 | 27.5±0.84 | 26.1±0.86 | 24.0±1.03** | | 13.7±1.47*** |
| 14 | 26.5±0.67 | 25.8±0.84 | 25.4±0.92 | 26.1±1.21 | | 23.0±1.30* |
| 15 | 26.5±0.84 | 25.4±1.02 | 24.5±0.99 | 24.2±0.96 | | 26.5±0.88 |
| 16 | 26.9±0.81 | 27.4±0.92 | 26.2±0.94 | 24.8±1.13 | | 25.6±0.97 |
| 17 | 27.5±0.94 | 29.0±0.74 | 27.8±0.70 | 29.3±0.96 | | 25.4±1.12 |
| 18 | 29.0±0.56 | 28.8±0.96 | 30.1±0.76 | 30.2±0.83 | | 27.3±1.14 |
| 19 | 28.1±0.81 | 28.8±0.75 | 28.9±0.72 | 30.0±0.70 | | 25.4±1.34 |
| 20 | 25.5±0.91 | 28.4±1.04* | 27.8±0.97 | 28.8±0.78*** | | 24.4±1.22 |
| 21 | 18.5±1.01 | 20.7±1.63 | 19.3±0.84 | 23.6±0.89*** | | 18.6±1.14 |

** p<0.05 ** p<0.01 *** p<0.001 (Student's t-test)*

The results of laparotomies are summarized in Table C.1.2.7. The significant decrease in the mean number of corpora lutea in the 100 mg/kg group ($p<0.05$), and the non-significant increases in the rate of implantation in the 100 and 300 mg/kg groups were not considered to be treatment-related, since treatment did not begin until day 6 of gestation. The proportion of fetuses alive at the time of sacrifice of the dams was only 4% lower in the 300 mg/kg group than in the vehicle control group, but this difference was statistically significantly ($p<0.05$). This effect was interpreted by the study authors as being due to administration of quizalofop-ethyl. The increase in retained placenta in the 300 mg/kg group ($p<0.05$) was also considered to be treatment-related.

Table C.1.2.7. Observations of Uterine Contents from Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg | 60000 IU Vitamin A (positive control) |
| Number of dams | 21 | 21 | 22 | 24 | 20 |
| Number of corpora lutea (mean ± S.D.) | 375 (17.9±0.44) | 358 (17.0±0.51) | 360 (16.4±0.48)* | 415 (17.3±0.43) | 365 (18.3±0.54) |
| Number of implantations (mean ± S.D.) | 342 (91.2%) (16.3±0.48) | 318 (88.8%) (15.1±0.72) | 347 (96.4%) (15.8±0.43) | 394 (94.9%) (16.4±0.43) | 309 (84.7%)* (15.5±0.72) |
| Number of live fetuses (mean ± S.D.) | 329 (96.2%) (15.7±0.47) | 308 (96.9%) (14.7±0.70) | 331 (95.4%) (15.0±0.41) | 361 (91.6%)* (15.0±0.44) | 74 (23.9%)*** (6.7±1.47) |
| Number of live male fetuses (mean ± S.D.) | 152 (46.2%) (7.2±0.38) | 164 (53.3%) (7.8±0.61) | 162 (49.0%) (7.4±0.56) | 182 (50.4%) (7.6±0.43) | 40 (54.1%) (4.4±0.87) |
| Number of live female fetuses (mean ± S.D.) | 177 (53.8%) (8.4±0.48) | 144 (46.8%) (6.9±0.48)* | 169 (51.1%) (7.7±0.58) | 179 (49.6%) (7.5±0.55) | 34 (45.9%) (3.8±0.92)*** |
| Number of immature fetuses | 0 | 0 | 0 | 0 | 0 |
| Number of dead fetuses | 0 | 0 | 0 | 0 | 0 |
| Resorptions | | | | | |
| Implantation scar | 2 (0.6%) | 4 (1.3%) | 0 | 1 (0.3%) | 81 (26.2%)*** |
| Retained placenta | 10 (2.9%) | 4 (1.3%) | 15 (4.3%) | 25 (6.4%)* | 127 (41.1%)*** |
| Early resorption | 1 (0.3%) | 2 (0.6%) | 1 (0.3%) | 6 (1.5%) | 26 (8.4%)*** |
| Late resorption | 0 | 0 | 0 | 1 (0.3%) | 1 (0.3%) |
| Macerated embryo | 0 | 0 | 0 | 0 | 0 |
| Malformations | 0 | 2 (0.6%) | 0 | 0 | 74 (100%)*** |
| Fetal body weight (g) | | | | | |
| Male (mean ± S.D.) | 5.28±0.05 | 5.36±0.07 | 5.48±0.05* | 5.24±0.08 | 4.24±0.21*** |
| Female (mean ± S.D.) | 5.01±0.05 | 5.07±0.08 | 5.16±0.06 | 4.94±0.08 | 4.13±0.17*** |

** p<0.05 ** p<0.01 *** p<0.001 (Student's t-test for means, chi-square test for percentages)*

The only external malformations noted in vehicle controls or quizalofop-ethyl-treated fetuses occurred in the 30 mg/kg group, where the lack of a tail in two animals was not considered to be due to quizalofop-ethyl. None of the visceral abnormalities observed appeared to be related to treatment with quizalofop-ethyl, with the possible exception of a non-significant increase in incidence of pyelectasis in the 300 mg/kg group. The slight increase in overall incidence of malformed fetuses in the 300 mg/kg group was also not statistically significant (Table C.1.2.8).

Table C.1.2.8. Results of Fetal Visceral Examinations from Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (dams) | | | | | |
|---|---|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg | | 60000 IU Vitamin A (positive control) |
| Number of dams | 21 | 21 | 22 | 24 | | 7 |
| Number of fetuses examined | 162 | 151 | 162 | 173 | | 36 |
| Number of dams with fetuses with visceral malformations (%) | 3 (14.3) | 4 (19.07) | 4 (18.2) | 6 (25.0) | | 7 (100)*** |
| Number of fetuses with visceral abnormality (%) | 3 (1.9) | 4 (2.6) | 4 (2.5) | 9 (5.2) | | 36 (100)*** |
| Malformations (%) | | | | | | |
| Hemopericardium | 0 | 1 (0.7) | 0 | 2 (1.2) | | 1 (2.8) |
| Rotation of heart to the left | 0 | 0 | 1 (0.6) | 0 | | 0 |
| Pyelectasis | 3 (1.9) | 3 (2.0) | 3 (1.9) | 6 (3.5) | | 10 (27.8)*** |
| Nephredema | 0 | 0 | 0 | 0 | | 15 (41.7)*** |
| Uraniscochasm | 0 | 0 | 0 | 0 | | 33 (91.7)*** |
| Diaphragmatic hernia | 0 | 0 | 1 (0.6) | 1 (0.6) | | 0 |

****p<0.001 (Student's t-test for means, chi-square test for percentages)*

While no skeletal abnormalities were observed in fetuses exposed to quizalofop-ethyl, there was a significant increase in the number of fetuses in the 300 mg/kg group that showed skeletal variations ($p<0.001$) (Table C.1.2.9).

Table C.1.2.9. Results of Fetal Skeletal Examinations from Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (dams) | | | | | |
|---|---|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg | | 60000 IU Vitamin A (positive control) |
| Number of dams | 21 | 21 | 22 | 24 | | 11 |
| Number of fetuses examined | 167 | 157 | 169 | 188 | | 38 |
| Number of dams with fetuses showing skeletal variations (%) | 16 (76.2) | 14 (66.7) | 18 (81.8) | 23 (95.8) | | 9 (81.8) |
| Number of fetuses with skeletal variations (%) | 49 (29.3) | 54 (34.3) | 60 (35.5) | 91 (48.4)*** | | 23 (60.5)*** |
| Corpus and arcus of lumbar vertebra 1-6 | 165 (98.8) | 149 (94.9) | 158 (93.5) | 185 (98.4) | | 1 (2.6)*** |
| 1-7 | 2 (1.2) | 8 (5.1) | 11 (6.5)* | 3 (1.6) | | 6 (15.8)*** |
| Cervical rib | 0 | 0 | 0 | 0 | | 3 (7.9)** |
| Fourteen-rib, unilateral | 27 (16.2) | 27 (17.2) | 22 (13.0) | 38 (20.2) | | 4 (10.5) |
| Fourteen-rib, bilateral | 22 (13.2) | 27 (17.2) | 38 (22.5)* | 53 (28.2)*** | | 14 (36.8)*** |
| Fourteen-rib, total | 49 (29.4) | 54 (34.4) | 60 (35.5) | 92 (48.4)*** | | 18 (47.3)*** |

** p<0.05 ** p<0.01 *** p<0.001*
*(Student's t-test for means, chi-square test for percentages)*

For pregnant animals that were allowed to deliver and nurse their young, weight gain during gestation and lactation is summarized in Table C.1.2.10. All of these animals gave birth to live young. Weight gain for the period between days 6-15 of gestation was significantly reduced in the 100 mg/kg ($p<0.05$) and 300 mg/kg ($p<0.001$) groups, and mean body weights on days 8, 10-12 and 14-16 in the 300 mg/kg group ($p<0.05$ for each day). In addition, body weights during weeks one and three of lactation were significantly lower in the 300 mg/kg group ($p<0.05$), and in the 100 mg/kg group during week two of lactation ($p<0.05$), although weight gain throughout the lactational period was unaffected in both groups. Food intake was also sporadically decreased in animals in the 100 mg/kg and 300 mg/kg groups during gestation, as summarized in Table C.1.2.11. Food intake during lactation was not significantly affected. Absolute organ weights of dams at weaning were also affected only sporadically, with effects only observed in the 30 mg/kg group. Relative to controls, brain weight was reduced by 6.3% ($p<0.05$), heart weight by 7.3% ($p<0.05$) and urinary bladder by 7.1% ($p<0.05$). Relative weight (organ weight/body weight) of the uterus was increase by 14.3% ($p<0.05$) in the 30 mg/kg group compared to controls, and the relative weight of the right adrenal gland was increased by

14.4% in the 100 mg/kg group ($p<0.01$); the relative weight of the left adrenal gland was unaffected.

Table C.1.2.10. Body Weight Gain over the Gestational and Lactational Periods in Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group | | | |
|---|---|---|---|---|
| Day of Gestation | 0 mg/kg (vehicle control) (n=14) | 30 mg/kg (n=13) | 100 mg/kg (n=13) | 300 mg/kg (n=14) |
| 0 | 252.3±3.70[a] | 248.9±4.25 | 255.2±5.07 | 250.4±3.22 |
| 6 | 279.4±2.87 | 275.2±4.73 | 282.5±5.47 | 279.0±2.97 |
| 7 | 284.0±3.31 | 278.2±4.31 | 280.9±5.56 | 275.6±3.39 |
| 8 | 285.7±3.06 | 278.2±4.60 | 281.1±5.46 | 275.1±3.42* |
| 9 | 287.7±3.28 | 281.2±4.90 | 283.7±5.47 | 278.1±3.32 |
| 10 | 296.3±4.14 | 287.8±5.16 | 288.2±5.98 | 282.7±2.91* |
| 11 | 301.3±4.12 | 294.3±5.73 | 291.2±5.91 | 289.4±3.95* |
| 12 | 306.9±4.03 | 298.9±5.77 | 294.6±6.68 | 295.4±3.77* |
| 13 | 311.6±4.42 | 304.2±5.81 | 301.2±6.07 | 299.3±4.06 |
| 14 | 318.1±4.51 | 309.8±5.85 | 307.5±5.72 | 304.1±3.95* |
| 15 | 323.0±4.06 | 316.6±6.43 | 318.3±6.33 | 309.3±4.28* |
| 16 | 332.6±4.38 | 327.8±6.84 | 329.5±6.40 | 318.1±4.66* |
| 17 | 347.3±5.01 | 342.5±6.96 | 345.2±6.32 | 333.9±4.90 |
| 18 | 361.9±5.44 | 360.9±7.73 | 360.9±7.40 | 353.3±5.97 |
| 19 | 376.6±5.97 | 376.0±8.16 | 380.2±7.86 | 372.4±6.17 |
| 20 | 393.1±5.44 | 394.0±8.19 | 396.8±8.28 | 388.4±6.96 |
| 21 | 405.1±7.4 | 406.8±9.6 | 410.0±8.5 | 400.9±6.8 |
| Days 0-21 (gain) | 151.7±7.25 | 157.8±7.65 | 154.8±5.26 | 150.4±5.13 |
| Days 6-21 (gain) | 125.7±6.34 | 131.5±5.58 | 127.5±4.27 | 121.9±4.90 |
| Days 6-15 (gain) | 43.6±2.58 | 41.4±2.15 | 35.8±1.86* | 30.3±2.38*** |
| Week of Lactation | | | | |
| 0 | 301.3±5.82 | 299.7±6.70 | 291.4±9.36 | 287.7±6.54 |
| 1 | 317.9±4.26 | 310.6±5.46 | 309.1±6.11 | 304.1±4.49* |
| 2 | 326.1±4.75 | 322.0±5.72 | 308.5±4.40* | 319.1±4.64 |
| 3 | 322.3±4.86 | 311.8±5.92 | 310.9±4.38 | 308.0±4.32* |
| Week 0-3 (gain) | 21.0±4.88 | 12.2±3.30 | 19.5±8.21 | 20.3±5.16 |

[a] *Mean body weight (g) ± S.E.* * $p<0.05$ *** $p<0.001$ *(Student's t-test)*

Table C.1.2.11. Food Intake over the Gestational and Lactational Periods by Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group | | | |
|---|---|---|---|---|
| Day of Gestation | 0 mg/kg (vehicle control) (n=14) | 30 mg/kg (n=13) | 100 mg/kg (n=13) | 300 mg/kg (n=14) |
| 0-6 | 21.7±0.51[a] | 21.0±0.55 | 22.1±0.73 | 21.6±0.48 |
| 7 | 22.3±0.66 | 21.1±0.74 | 19.4±0.73** | 17.9±1.08** |
| 8 | 23.1±1.02 | 22.0±0.88 | 19.4±0.97* | 16.1±0.74*** |
| 9 | 22.9±1.16 | 21.8±0.95 | 20.5±0.99 | 17.0±0.81*** |
| 10 | 23.1±1.02 | 20.6±0.89 | 19.7±0.90* | 20.6±1.18 |
| 11 | 23.6+1.36 | 20.8+0.77 | 18.9±0.98* | 20.4±1.07 |
| 12 | 24.3±1.26 | 21.2±0.77 | 20.0±1.11* | 21.0±0.98* |
| 13 | 24.3±1.00 | 22.3±0.90 | 21.2±0.70* | 22.7±1.27 |
| 14 | 25.4±0.95 | 23.7±0.90 | 22.0±1.15* | 22.6±1.27 |
| 15 | 24.1±0.80 | 22.3±0.98 | 23.5±0.85 | 21.0±1.51 |
| 16 | 25.4±1.01 | 24.5±0.82 | 25.7±1.11 | 22.4±1.33 |
| 17 | 26.9±1.04 | 24.9±0.87 | 27.8±0.92 | 26.9±1.00 |
| 18 | 28.6±0.90 | 27.5±1.30 | 29.4±1.35 | 28.4±0.96 |
| 19 | 28.3±1.05 | 27.8±0.83 | 30.2±1.21 | 30.4±1.03 |
| 20 | 26.9±0.91 | 27.1±0.89 | 28.8±1.31 | 29.6±1.21 |
| 21 | 23.6±1.50 | 22.9±1.35 | 23.7±2.02 | 25.0±1.32 |
| Days of Lactation | | | | |
| 0-7 | 37.1±0.94 | 36.6±0.83 | 38.4±1.04 | 36.7±1.19 |
| 8-14 | 52.1±1.37 | 53.5±0.63 | 55.3±1.10 | 53.1±0.90 |
| 15-21 | 60.7±1.19 | 60.5±0.71 | 63.6±1.25 | 58.8±1.20 |

[a]*Mean Food Intake (g) ± S.E.  * p<0.05  ** p<0.01  *** p<0.001  (Student's t-test)*

The outcome of parturition in these dams is summarized in Table C.1.2.12. The only statistically significant effect was a slight increase in the proportion of male pups in litters from the 300 mg/kg dams (57.5%) compared to controls (47.2%) ($p<0.05$). The corresponding proportions of female pups in these groups (42.5% and 52.8%, respectively) did not differ significantly. The only external abnormality observed in the pups was a single incidence of short tail in a pup from the 300 mg/kg group.

Table C.1.2.12. Outcome of Parturition in Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg |
| Number of pregnant animals | 14 | 13 | 13 | 14 |
| Number of animals giving birth to young | 14 (100%) | 13 (100%) | 13 (100%) | 14 (100%) |
| Period of pregnancy (days) | 21.4±0.14 | 21.3±0.13 | 21.5±0.14 | 21.3±0.13 |
| Total number of implantation sites (litter mean ± S.E.) | 211 | 206 | 217 | 231 |
| Number of young born (litter mean ± S.E.) | 193 (91.5%) (13.8±0.84) | 191 (92.7%) (14.7±0.51) | 198 (91.2%) (15.2±0.53) | 214 (92.6%) (15.3±0.38) |
| Number of live young (litter mean ± S.E.) | 193 (100%) | 191 (100%) | 198 (100%) | 214 (100%) |
| Number of live male young (litter mean ± S.E.) | 91 (47.2%) (7.3±0.52) | 96 (50.3%) (7.4±0.67) | 94 (47.5%) (7.2±0.41) | 123 (57.5%) (8.8±0.59)* |
| Number of live female young (litter mean ± S.E.) | 102 (52.8%) (7.3±0.52) | 95 (49.7%) (7.3±0.77) | 104 (52.5%) (8.0±0.51) | 91 (42.5%) (6.5±0.44) |
| Number of stillborn young | 0 | 0 | 0 | 0 |
| Number of young with external abnormality | 0 | 0 | 0 | 1 (0.5%) |
| Body weight of live young (g) | | | | |
| Male (mean ± S.E.) | 6.14±0.13 | 6.07±0.13 | 5.90±0.10 | 5.87±0.08 |
| Female (mean ± S.E.) | 5.80±0.13 | 5.69±0.12 | 5.53±0.12 | 5.49±0.08 |

** $p<0.05$ (Student's t-test)*

Litters were reduced randomly to four male and four female pups, as far as possible, on day four of lactation. There were no significant differences in pup survival either before or after reduction in litter size. Pup survival up to reduction in litter size was 96.9%, 97.4%, 96.5% and 94.4% in 0, 30, 100 and 300 mg/kg groups, respectively. After reduction in litter size, survival until 8 weeks of age was 100%, 99.0%, 100% and 98.2%,

respectively. One pup in the 30 mg/kg group died on day 21 postnatal, and two pups in the 300 mg/kg group died, one on each of days 6 and 11 postnatal. Body weights and

Table C.1.2.13. Postnatal Body Weight Gain in Rat Pups from Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (dams) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Day Postnatal | 0 mg/kg (vehicle control) | | 30 mg/kg | | 100 mg/kg | | 300 mg/kg | |
| | Male | Female | Male | Female | Male | Female | Male | Female |
| 0 | 6.14 ± 0.13 [a] | 5.80 ± 0.13 | 6.03 ± 0.14 | 5.69 ± 0.12 | 5.90 ± 0.10 | 5.53 ± 0.12 | 5.87 ± 0.08 | 5.49 ± 0.08 |
| 4 (before reduction) | 9.61 ± 0.39 | 9.10 ± 0.39 | 9.09 ± 0.36 | 8.47 ± 0.25 | 9.03 ± 0.24 | 8.53 ± 0.23 | 8.58 ± 0.18* | 8.12 ± 0.21* |
| 4 (after reduction) | 9.93 ± 0.35 | 9.41 ± 0.36 | 9.35 ± 0.33 | 8.64 ± 0.19 | 9.38 ± 0.22 | 8.99 ± 0.22 | 9.06 ± 0.20* | 8.43 ± 0.22* |
| Week Postnatal | | | | | | | | |
| 1 | 15.98 ±0.52 | 15.17 ±0.51 | 15.13 ±0.50 | 14.49 ±0.38 | 15.54 ±0.46 | 14.81 ±0.47 | 14.70 ±0.24 | 13.75 ±0.21* |
| 2 | 32.66 ±1.05 | 31.03 ±1.08 | 31.79 ±0.60 | 30.41 ±0.46 | 30.16 ±1.34 | 30.31 ±1.13 | 31.15 ±0.54 | 29.79 ±0.45 |
| 3 | 51.70 ±1.22 | 49.26 ±1.24 | 49.82 ±1.04 | 47.54 ±0.73 | 51.92 ±1.18 | 49.92 ±1.33 | 49.56 ±0.87 | 46.85 ±0.57 |
| 4 | 94.18 ±1.91 | 85.73 ±1.67 | 90.32 ±1.89 | 82.25 ±0.89 | 92.81 ±1.96 | 86.50 ±2.09 | 89.17 ±1.43* | 80.63 ±0.72** |
| 5 | 146.00 ±2.80 | 126.96 ±2.19 | 139.03 ±2.71 | 121.58 ±1.35 | 143.65 ±2.47 | 126.81 ±2.79 | 138.00 ±1.91* | 119.91 ±1.16** |
| 6 | 203.59 ±3.54 | 161.43 ±1.96 | 197.71 ±3.25 | 157.02 ±1.78 | 201.88 ±2.90 | 161.27 ±2.93 | 195.71 ±2.49 | 157.39 ±1.46 |
| 7 | 256.95 ±3.38 | 185.69 ±2.10 | 252.45 ±3.49 | 176.14 ±4.28 | 255.46 ±3.58 | 184.46 ±3.02 | 250.68 ±3.35 | 182.06 ±1.70 |
| 8 | 311.81 ±4.02 | 208.94 ±2.43 | 304.48 ±4.18 | 202.66 ±2.63 | 303.92 ±4.57 | 206.65 ±3.53 | 299.60 ±3.88* | 203.71 ±2.16 |
| Week 0-3 (gain) | 45.57 ±1.13 | 43.46 ±1.16 | 43.79 ±0.95 | 41.85 ±0.65 | 46.03 ±1.12 | 44.40 ±1.24 | 43.69 ±0.82 | 41.36 ±0.57 |
| Week 3-8 (gain) | 260.11 ±3.26 | 159.69 ±2.21 | 254.66 ±3.88 | 155.15 ±2.74 | 252.00 ±3.92 | 156.73 ±2.80 | 250.04 ±3.69 | 156.86 ±2.46 |

[a] *Mean body weight (g) ± S.E. * $p<0.05$ ** $p<0.01$ (Student's t-test)*
*Although the total number of pups is reported at each timepoint, the numbers of male and female pups are not reported. It appeared that there were approximately 52-55 pups of each gender in each treatment group after litter size was reduced on postnatal day 4.*

weight gain of male and female pups during the first eight weeks postnatal are summarized in Table C.1.2.13. Male pups whose dams were exposed to 300 mg/kg were significantly lighter than controls on day 4 postnatal (before and after reduction in litter size), and at weeks 4, 5 and 8 postnatal ($p<0.05$ in all cases), although net weight gain over the 8 week period was not significantly reduced. Female pups whose dams were exposed to 300 mg/kg were also significantly lighter than controls on day 4 postnatal (before and after reduction in litter size) ($p<0.05$), and at weeks 1 ($p<0.05$), 4 and 5 postnatal ($p<0.01$). Again, there was no significant difference in net weight gain over this period. Food intake by both male and female pups from this group was also significantly reduced at most timepoints between weeks 4 and 8 postnatal (Table C.1.2.14).

Table C.1.2.14. Postnatal Food Intake by Rat Pups from Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (dams) | | | |
|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg |
| Males | | | | |
| Week postnatal | | | | |
| 4 | 10.15±0.21[a] | 9.83±0.29 | 10.14±0.31 | 9.46±0.24* |
| 5 | 17.46±0.33 | 16.81±0.33 | 16.91±0.45 | 16.25±0.24** |
| 6 | 22.17±0.39 | 21.48±0.49 | 21.93±0.30 | 21.16±0.26* |
| 7 | 26.57±0.40 | 26.05±0.40 | 26.37±0.32 | 25.48±0.39 |
| 8 | 28.54±0.33 | 28.00±0.44 | 27.78±0.36 | 27.15±0.37** |
| Females | | | | |
| Week postnatal | | | | |
| 4 | 9.34±0.23 | 8.88±0.15 | 9.54±0.32 | 8.56±0.23* |
| 5 | 15.47±0.26 | 15.76±0.18 | 15.37±0.32 | 14.13±0.27** |
| 6 | 17.97±0.39 | 17.48±0.22 | 17.88±0.29 | 17.26±0.21 |
| 7 | 19.73±0.34 | 18.92±0.27 | 19.32±0.30 | 19.04±0.29 |
| 8 | 20.21±0.40 | 20.00±0.36 | 19.63±0.47 | 19.01±0.30* |

[a]*Mean Daily Food Intake (g) ± S.E.* * $p<0.05$ ** $p<0.01$ *(Student's t-test)*

There were no significant differences between groups of pups in general development as assessed by dates of attainment of developmental landmarks described in the study report as dilation of auricles, hair development of skin, budding of incisors, separation of eyelids, descent of testes or opening of vagina. Assessment of spontaneous activity in an open field and number of errors in a swim maze over three trials also revealed no indications of differences between the groups; these behavioral tests were carried out when the pups were 3-4 weeks of age.

Table C.1.2.15. Absolute and Relative Organ Weights at Age 8 Weeks in Rat Pups from Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (dams) | | | |
|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg |
| Males | | | | |
| Lung – absolute (g) | 1.50±0.02[a] | 1.50±0.02 | 1.52±0.02 | 1.54±0.02 |
| Lung – relative (g%) | 0.48±0.01 | 0.49±0.01 | 0.50±0.01 | 0.51±0.01* |
| Liver – absolute (g) | 18.32±0.51 | 17.53±0.39 | 17.26±0.38 | 17.06±0.28* |
| Liver – relative (g%) | 5.89±0.13 | 5.75±0.08 | 5.65±0.11 | 5.67±0.08 |
| Right Kidney – absolute (g) | 1.53±0.04 | 1.47±0.03 | 1.48±0.03 | 1.44±0.03 |
| Right Kidney – relative (g%) | 0.49±0.01 | 0.48±0.01 | 0.48±0.01 | 0.48±0.01 |
| Left Kidney – absolute (g) | 1.51±0.03 | 1.44±0.03 | 1.45±0.03 | 1.41±0.03* |
| Left Kidney – relative (g%) | 0.49±0.01 | 0.47±0.01 | 0.48±0.01 | 0.47±0.01 |
| Heart – absolute (g) | 1.10±0.02 | 1.06±0.02 | 1.08±0.02 | 1.05±0.02 |
| Heart – relative (g%) | 0.36±0.01 | 0.35±0.01 | 0.35±0.01 | 0.35±0.01 |
| Females | | | | |
| Lung – absolute (g) | 1.20±0.03 | 1.27±0.06 | 1.20±0.01 | 1.21±0.03 |
| Lung – relative (g%) | 0.58±0.02 | 0.63±0.03 | 0.58±0.01 | 0.59±0.01 |
| Liver – absolute (g) | 11.57±0.26 | 10.93±0.22 | 11.12±0.22 | 11.32±0.20 |
| Liver – relative (g%) | 5.60±0.11 | 5.38±0.07 | 5.35±0.07 | 5.49±0.06 |
| Right Kidney – absolute (g) | 1.03±0.02 | 1.01±0.02 | 1.04±0.02 | 0.97±0.02* |
| Right Kidney – relative (g%) | 0.50±0.01 | 0.50±0.01 | 0.50±0.01 | 0.47±0.01* |
| Left Kidney – absolute (g) | 1.00±0.02 | 0.98±0.02 | 1.00±0.02 | 0.95±0.02 |
| Left Kidney – relative (g%) | 0.49±0.01 | 0.48±0.01 | 0.48±0.01 | 0.46±0.01 |
| Heart – absolute (g) | 0.82±0.02 | 0.79±0.01 | 0.77±0.01 | 0.77±0.01 |
| Heart – relative (g%) | 0.40±0.01 | 0.39±0.01 | 0.37±0.01* | 0.37±0.01 |
| Uterus – absolute (g) | 0.47±0.03 | 0.42±0.02 | 0.44±0.03 | 0.39±0.02** |
| Uterus – relative (g%) | 0.23±0.01 | 0.20±0.01 | 0.21±0.01 | 0.19±0.01* |

[a] *Mean body weight (g) ± S.E.* * $p<0.05$ ** $p<0.01$ *(Student's t-test)*
*The total number of male and female pups from each treatment group from which organs were harvested is not reported.*

At age 8 weeks, all but two male and two female pups from each litter were sacrificed, and thoracic organs were removed and weighed (thyroid, thymus, heart, lung, liver, spleen, pancreas, kidney, adrenal gland, testis, prostate, seminal vesicle, ovary, uterus, urinary bladder). Absolute and relative weights of organs where there was a statistically significant difference between control and treated animals are summarized in Table C.1.2.15. There appeared to be no treatment-related effects on weights of any other organs examined. The study authors concluded that the statistically significant effects on organ weights were not related to treatment, since they did not occur in the dams

administered directly with quizalofop-ethyl. The study authors did not discuss the difference in developmental stage between pups and dams at the time of exposure.

The results of skeletal examinations of pups at age 8 weeks are summarized in Table C.1.2.16. No skeletal abnormalities were observed in any pups. The incidence of skeletal variations was significantly lower in all treatment groups than in controls.

Table C.1.2.16. Skeletal Examination at Age 8 Weeks of Rat Pups from Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (dams) | | | |
|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg |
| Number of dams | 14 | 13 | 13 | 14 |
| Number of young examined | 53 | 51 | 52 | 54 |
| Number of dams with young showing skeletal abnormalities | 0 | 0 | 0 | 0 |
| Number of young showing skeletal abnormalities | 0 | 0 | 0 | 0 |
| Number of dams with young showing skeletal variations | 11 (78.6)[1] | 5 (38.5) | 6 (46.2) | 8 (57.1) |
| Number of young with skeletal variations | 19 (35.8) | 9 (17.6)* | 9 (17.3)* | 9 (16.7)* |
| Fourteen-rib, unilateral | 3 (5.7) | 2 (3.9) | 0 | 4 (7.4) |
| Fourteen-rib, bilateral | 3 (5.7) | 0 | 1 (1.9) | 1 (1.9) |
| Seven lumbar vertebrae | 1 (1.9) | 0 | 0 | 0 |
| Excess of fifth sternebra | 15 (28.3) | 7 (13.7) | 8 (15.4) | 5 (9.3)* |

** $p<0.05$ (Student's t-test for means, chi-square test for percentages)*
*[1] percentage of examined animals affected*

The two male and two female pups from each litter that were not sacrificed at age 8 weeks were used in a test of reproductive ability at age 10 weeks. Male and female pairs were established within treatment groups, with sibling pairs being avoided. Pairs were co-housed for 10 days for breeding. If the female did not become pregnant, breeding was repeated as follows: for the male, an untreated multiparous female was added to the pair for 10 days; if the male failed to mate or induce pregnancy in one of the females, he was paired with two different females for another 10 days. The female from the original pair was paired for 10 days with a male which had proven reproductive ability from the same treatment group. If no such male was available, the female was paired with an untreated male of proven breeding ability. If pregnancy did not result, the process was repeated for a further 10 days with a different male.

Table C.1.2.17. Test of Reproductive Ability in Offspring of Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg |
| Number of animals used | | | | |
| Males | 28 | 26 | 26 | 28 |
| Females | 28 | 26 | 26 | 28 |
| First breeding | | | | |
| Pairs of animals with reproductive ability confirmed | 26 (92.9%) | 20 (76.9%) | 24 (92.3%) | 25 (89.3%) |
| Pairs of animals with reproductive ability not confirmed | 2 | 6 | 2 | 3 |
| Second breeding | | | | |
| Animals with reproductive ability confirmed | | | | |
| Males | 2 | 5 | 2 | 2 |
| Females | 2 | 5 | 2 | 3 |
| Total | | | | |
| Males | 28 (100%) | 25 (96.2%) | 26 (100%) | 27 (96.4%) |
| Females | 28 (100%) | 25 (96.2%) | 26 (100%) | 28 (100%) |
| Third breeding | | | | |
| Animals with reproductive ability confirmed | | | | |
| Males | - | 0 | - | 0 |
| Females | - | 0 | - | 0 |
| Total | | | | |
| Males | 28 (100%) | 25 (96.2%) | 26 (100%) | 27 (96.4%) |
| Females | 28 (100%) | 25 (96.2%) | 26 (100%) | 28 (100%) |
| Animals with reproductive ability not confirmed | | | | |
| Males | 0 | 0* | 0 | 1 (3.6%) |
| Females | 0 | 0* | 0 | 0 |
| Number of estrous periods required for pregnancy $\pm$ S.E. | 1.1 $\pm$ 0.10 | 1.6 $\pm$ 0.22 | 1.3 $\pm$ 0.15 | 1.5 $\pm$ 0.18 |

** As shown in the study report. The earlier entry of 25/26 males and 25/26 females identified as having confirmed breeding ability suggests that these entries should both be 1 (3.8%).*

The results of the test of reproductive ability are summarized in Table C.1.2.17. There were no significant differences in reproductive ability between the control and any of the treatment groups.

For female rats that became pregnant in the course of the test of reproductive ability, body weight and food consumption were measured on days 0, 7, 14 and 21 of gestation, and all of these animals were sacrificed on day 21 of gestation. Changes in body weight and food consumption are summarized in Table C.1.2.18. Body weights were significantly lower in the 30 mg/kg females than in controls at days 0 and 7 of gestation ($p<0.05$), while no significant differences were observed between controls and 100 or 300 mg/kg animals. No significant differences in food consumption were observed.

Table C.1.2.18. Body Weight Gain and Food Intake over Gestation by Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group | | | |
|---|---|---|---|---|
| Day of Gestation | 0 mg/kg (vehicle control) (n=28) | 30 mg/kg (n=25) | 100 mg/kg (n=26) | 300 mg/kg (n=28) |
| Body Weight | | | | |
| 0 | 253.6±3.89[a] | 240.8±3.77* | 248.8±4.25 | 249.7±3.72 |
| 7 | 283.2±4.44 | 271.2±3.31* | 281.6±4.19 | 279.9±3.63 |
| 14 | 320.5±4.76 | 311.0±4.07 | 322.5±4.63 | 320.1±4.12 |
| 21 | 429.8±7.74 | 415.0±5.70 | 426.2±6.45 | 429.9±5.66 |
| Days 0-21 (gain) | 176.1±5.62 | 174.2±4.17 | 174.4±4.17 | 180.2±3.50 |
| Food Intake | | | | |
| 1-7 | 160.1 (22.87)[b] ± 3.44 | 153.4 (21.91) ± 2.51 | 158.8 (22.68) ± 3.57 | 153.9 (21.99) ± 2.60 |
| 8-14 | 194.7 (27.81) ± 3.77 | 187.4 (26.77) ± 3.11 | 192.9 (27.56) ± 4.54 | 193.2 (27.60) ± 3.96 |
| 15-21 | 204.1 (29.16) ± 4.66 | 202.3 (28.90) ± 3.46 | 200.5 (28.64) ± 4.01 | 205.3 (29.33) ± 3.50 |

[a] *Mean Body Weight (g) ± S.E. * $p<0.05$ (Student's t-test)*
[b] *Mean Total (Daily) Food Intake (g) ± S.E*

The results of fetal examinations following the test of reproductive ability are summarized Table C.1.2.19. There were no significant differences between control and any treatment groups in any of the parameters reported.

Organ weights were recorded for animals that had been successful in the test of reproductive ability. Organs were taken at the time of laparotomy for females and at age 22 weeks for males. The results for organs where significant differences were reported in

either sex are summarized in Table C.1.2.20. None of the statistically significant effects were considered to be treatment-related by the study authors. Reproductive organs from animals which had been unsuccessful in the test of reproductive ability were removed at the same timepoints, and were examined histopathologically. No data resulting from the histopathological examination were provided for these organs, but it was reported that nothing abnormal was found in them.

Table C.1.2.19. Outcome of Parturition Following Test of Reproductive Ability of Offspring of Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (gestational exposure) | | | |
|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg |
| Number of dams | 28 | 25 | 26 | 28 |
| Number of corpora lutea (mean ± S.E.) | 443 (15.8±0.44) | 385 (15.4±0.40) | 405 (15.6±0.31) | 442 (15.8±0.24) |
| Number of implantation sites (mean ± S.E.) | 425 (95.9%) (15.2±0.65) | 380 (98.7%) (15.2±0.42) | 390 (96.3%) (15.0±0.40) | 434 (98.2%) (15.5±0.29) |
| Number of live fetuses (mean ± S.E.) | 414 (97.4%) (14.8±0.64) | 369 (97.1%) (14.8±0.61) | 381 (97.7%) (14.7±0.39) | 422 (98.2%) (15.1±0.30) |
| Number of live male fetuses (mean ± S.E.) | 205 (49.5%) (7.3±0.51) | 183 (49.6%) (7.3±0.50) | 200 (52.5%) (7.3±0.38) | 217 (51.4%) (7.8±0.39) |
| Number of live female fetuses (mean ± S.E.) | 209 (50.5%) (7.5±0.45) | 186 (50.4%) (7.4±0.52) | 181 (47.5%) (7.3±0.43) | 205 (48.6%) (7.3±0.38) |
| Number of immature fetuses | 1 (0.2%) | 0 | 2 (0.5%) | 0 |
| Number of dead fetuses | 0 | 0 | 0 | 0 |
| Number of resorptions | | | | |
| Implantation scar | 0 | 0 | 0 | 0 |
| Retained placenta | 11 (2.6%) | 10 (2.6%) | 7 (1.8%) | 11 (2.5%) |
| Early resorption | 0 | 1 (0.3%) | 0 | 1 (0.2%) |
| Late resorption | 0 | 0 | 0 | 0 |
| Macerated embryo | 0 | 0 | 2 (0.5%) | 0 |
| Malformations | 0 | 0 | 0 | 0 |
| Fetal body weight (g) | | | | |
| Male (mean ± S.E.) | 5.47±0.07 | 5.33±0.07 | 5.28±0.09 | 5.50±0.06 |
| Female (mean ± S.E.) | 5.15±0.06 | 5.02±0.06 | 5.00±0.10 | 5.11±0.05 |

Table C.1.2.20. Absolute and Relative Organ Weights in Male Rats Aged 22 Weeks and Female Rats at Laparotomy: Offspring of Female Rats Orally Exposed to Quizalofop-Ethyl on Days 6-15 of Gestation. (Nippon Experimental Medical Research Institute, 1983b).

| | Treatment Group (dams) | | | |
|---|---|---|---|---|
| | 0 mg/kg (vehicle control) | 30 mg/kg | 100 mg/kg | 300 mg/kg |
| Males | n=28 | n=26 | n=26 | n=28 |
| Final Body Weight (g) | 568.3±8.65[a] | 548.8±8.51 | 551.2±9.99 | 547.9±10.55 |
| Brain – absolute (g) | 2.11±0.02 | 2.05±0.02* | 2.06±0.02 | 2.02±0.02** |
| Brain – relative (g) | 0.37±0.01 | 0.38±0.01 | 0.38±0.01 | 0.37±0.01 |
| Right Adrenal gland – absolute (g) | 33.3±1.06 | 32.3±1.07 | 29.9±0.97* | 31.5±0.87 |
| Right Adrenal gland – relative (g) | 5.89±0.21 | 5.90±0.20 | 5.50±0.23 | 5.81±0.19 |
| Left Adrenal gland – absolute (g) | 35.9±1.10 | 33.8±0.99 | 32.0±0.98** | 33.6±0.87 |
| Left Adrenal gland – relative (g) | 6.36±0.21 | 6.24±0.15 | 5.85±0.20 | 6.15±0.17 |
| Right Testis – absolute (g) | 1.84±0.03 | 1.89±0.03 | 1.81±0.05 | 1.86±0.03 |
| Right Testis – relative (g) | 0.33±0.01 | 0.35±0.01* | 0.33±0.01 | 0.34±0.01 |
| Left Testis – absolute (g) | 1.85±0.03 | 1.91±0.06 | 1.79±0.05 | 1.83±0.04 |
| Left Testis – relative (g) | 0.33±0.01 | 0.35±0.01 | 0.33±0.01 | 0.34±0.01 |
| Urinary Bladder – absolute (g) | 0.14±0.01 | 0.14±0.01 | 0.15±0.01 | 0.14±0.01 |
| Urinary Bladder – relative (g) | 0.03±0.001 | 0.03±0.001 | 0.03±0.001 | 0.03±0.002 |
| Females | n=28 | n=25 | n=26 | n=28 |
| Final Body Weight (g) | 429.8±7.74 | 415.0±5.70 | 426.2±6.45 | 429.9±5.66 |
| Brain – absolute (g) | 1.81±0.02 | 1.83±0.01 | 1.84±0.02 | 1.82±0.02 |
| Right Adrenal gland – absolute (g) | 34.6±1.20 | 38.0±1.29 | 38.6±1.42* | 33.5±1.22 |
| Left Adrenal gland – absolute (g) | 37.8±1.21 | 41.0±1.32 | 38.1±1.01 | 39.1±1.17 |
| Urinary Bladder – absolute (g) | 0.13±0.01 | 0.12±0.004* | 0.12±0.01 | 0.14±0.01 |

[a] *Mean ± S.E. * $p<0.05$ ** $p<0.01$ (Student's t-test)*

### *C.1.3 Other Relevant Data*

The general pharmacokinetics of quizalofop-ethyl in rats are described in section B.4. Quizalofop-ethyl is absorbed to a considerable extent after oral administration. Peak plasma or blood levels occur six to nine hours after administration, with decay around 20 to 30 hours. Quizalofop-ethyl and/or its metabolites are distributed to all tissues tested. No data on distribution to placenta or fetus were located. There is no indication, however, that quizalofop and/or its metabolites would not be distributed to the placenta or fetus.

### *C.1.4 Integrative Evaluation*

Two studies of the potential effects of quizalofop-ethyl on development were reviewed, one conducted in rabbits (Nippon Experimental Medical Research Institute, 1983a) and

the other conducted in rats (Nippon Experimental Medical Research Institute, 1983b). In both studies, quizalofop-ethyl was administered to pregnant females during the period of organogenesis for the species in question.

In the rabbit study (Nippon Experimental Medical Research Institute, 1983a), the highest dose tested (60 mg/kg/day) induced mild toxicity in the dams, but resulted in no apparent treatment-related adverse effects in the fetuses. The only effect to reach statistical significance was an increase in the proportion of female fetuses in the 30 mg/kg dose group, the second-highest dose tested. The corresponding decrease in proportion of male fetuses did not reach statistical significance, nor was there a significant effect at the highest dose tested.

The rat study (Nippon Experimental Medical Research Institute, 1983b) included both an evaluation of fetal effects at the end of the gestational period and postnatal evaluation of young that were delivered and suckled by their dams. There was a statistically significant decrease in the number of fetuses alive at the time of sacrifice of the dams on day 21 of gestation in the high dose group receiving 300 mg/kg/day quizalofop-ethyl, and a significant increase in the number of animals with retained placenta in the same group. The incidence of fetuses in the high dose (300 mg/kg/day) group showing skeletal variations was significantly higher than the control level ($p<0.001$), as was the number of fetuses showing bilateral and total (bilateral plus unilateral) incidence of $14^{th}$ ribs ($p<0.001$). There was also a significant increase in the incidence of bilateral $14^{th}$ ribs in fetuses of the 100 mg/kg/day dose group ($p<0.05$). A slight increase in the number of fetuses in the high dose group having visceral malformations did not achieve statistical significance.

The only statistically significant difference between control and treated offspring at parturition was a higher proportion of male pups in the 300 mg/kg/day group. As with the rabbit study above, the corresponding decrease in the proportion of the opposite sex was not statistically significant. Postnatal bodyweight in both male and female pups in the 300 mg/kg/day group was significantly lower than control values both pre and post-weaning, and food intake by these animals was also significantly lower than control values. Uterine weights in offspring assessed at age 8 weeks were significantly lower in offspring of 300mg/kg/day dams than in offspring of controls. Weights of liver and kidney were also significantly affected in both sexes at this dose level. Relative heart weight was significantly affected in female offspring of 100 mg/kg dams, while the same magnitude of effect in offspring of 300 mg/kg dams did not reach statistical significance. The study authors discounted these effects on organs weights as not being treatment-related because similar effects did not occur in the treated adults, but did not discuss the differing developmental stages at which exposure occurred.

There were no apparent effects on developmental landmarks such as incisor budding, hair eruption, descent of testicles or vaginal opening. Assessment of various behavioral indices also revealed no significant differences between treated and control animals. Breeding of male and female offspring at age 10 weeks did not show any differences between control and treated animals in reproductive parameters or in fetal development.

Body weight gain and food intake was significantly lower in the 100 and 300 mg/kg/day groups at various points during gestation and lactation, although the magnitude and distribution of the effect varied between the females scheduled for laparotomy and parturition.

## C.2. Female Reproductive Toxicity

### *C.2.1. Human Female Reproductive Toxicology Studies*

No studies or reports pertaining to female reproductive toxic effects of quizalofop-ethyl in humans were identified on the basis of comprehensive computerized literature searches.

### *C.2.2. Animal Female Reproductive Toxicology Studies*

Two subchronic feeding studies in dogs provided data on reproductive organ weights, and also assessed histopathology of the reproductive organs. The first of these studies (Nippon Experimental Medical Research Institute, 1982), was cited by U.S. EPA under TRI for male reproductive toxicity. A 90 day feeding study in rats, an 18 month feeding study in mice and a two year feeding study in rats also provided data on potential pathological effects on reproductive organs. None of these other studies were cited under TRI. A multigeneration reproduction study in rats cited under TRI and referenced in the U.S. EPA Integrated Risk Information Service (IRIS) could not be retrieved. Reproductive capability was also investigated in rats exposed to quizalofop-ethyl *in utero,* as discussed in Section C.1.2.

Subchronic feeding studies

**Nippon Experimental Medical Research Institute, 1982**. In this study cited by U.S. EPA under TRI for male reproductive toxicity and discussed below for that endpoint, beagle dogs were administered quizalofop-ethyl in feed for a period of 26 weeks. Both male and female dogs were included in the study, with 6 animals of each sex per treatment group. Animals were randomly distributed among groups, with the exception that siblings were not included in the same treatment group. Concentrations of quizalofop-ethyl in feed were 0 ppm (controls), 25 ppm, 100 ppm and 400 ppm; thus, a total of 24 male and 24 female animals were used. (The concentration of 100 ppm was reported to correspond to 3.20 mg/kg/day for males and 3.17 mg/kg/day for females, while the concentration of 400 ppm was reported to correspond to a 12.75 mg/kg/day for males and 12.39 mg/kg/day for females). Animals were approximately 7 months of age at the beginning of the treatment period. Food and water were available ad libitum, up to a maximum of 400 g/day of food per animal. Unconsumed food was measured daily, and water intake was measured over a 20 hour period once per week. Animals were observed twice per day for symptoms of toxicity, and were weighed weekly. Blood, stool and urine samples were collected monthly for analysis.

No animals died during the experimental period, and all animals were autopsied at the end of the experimental period. The study report states that, for histopathological examination, all organs were collected from 12 animals of both sexes, except the male and female genital organs which were harvested from six males or females (Note: the results of histopathological examination of ovaries total 6 animals/group). No other information is provided on how animals were selected for organ harvesting, or how the six males from which genital organs were harvested were distributed across the four experimental groups. Data for organ weights, including genital organs, are summarized on the basis of all experimental animals.

Tissues and organs that were used for histopathology were preserved in 10% buffered formalin. Results of histopathological examination of ovary, uterus and mammary gland are summarized in Table C.2.2.1. None of the histopathological effects noted for these organs were considered to be treatment-related.

Table C.2.2.1. Results of Histopathological Examination of Ovary, Uterus and Mammary Gland from Dogs Exposed to Quizalofop-Ethyl in Diet for 26 Weeks (Nippon Experimental Research Institute, 1982).

| | | Treatment Group | | | |
|---|---|---|---|---|---|
| Organ | Findings | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Ovary | Absence of corpora lutea | 3 | 3 | 5 | 1 |
| | Corpora lutea | 3 | 3 | 1 | 5 |
| Uterus | Congestion | 1 | 0 | 0 | 0 |
| | Immature | 3 | 1 | 2 | 1 |
| | Focal lymphocytic infiltration | 0 | 0 | 1 | 1 |
| | Small foci of hemorrhage | 0 | 0 | 1 | 0 |
| Mammary gland | Immature | 1 | 0 | 0 | 1 |
| | Dilated duct | 0 | 1 | 1 | 1 |

Ovarian and uterine weights are summarized in Table C.2.2.2. It was noted that ovary and uterus tended to decrease in absolute weight and relative weight to body weight in females of the 100 ppm dose group, but this was not indicated to be of statistical significance. The apparent increase in uterine weight in the 400 ppm group was also not indicated to be statistically significant. Data on relative organ weights were missing from all three copies of the study report obtained.

Table C.2.2.2. Ovarian and Uterine Weights from Dogs Exposed to Quizalofop-Ethyl in Diet for 26 Weeks (Nippon Experimental Research Institute, 1982).

| Treatment Group | N | Left Ovary (g) Mean ± S.D. | Right Ovary (g) Mean ± S.D. | Uterus (g) Mean ± S.D. |
|---|---|---|---|---|
| 0 ppm | 6 | 0.74 ± 0.35 | 0.71 ± 0.36 | 8.50 ± 6.97 |
| 25 ppm | 6 | 0.58 ± 0.23 | 0.73 ± 0.44 | 6.73 ± 6.02 |
| 100 ppm | 6 | 0.42 ± 0.06 | 0.40 ± 0.05 | 2.67 ± 0.66 |
| 400 ppm | 6 | 0.79 ± 0.33 | 0.67 ± 0.26 | 13.16 ± 9.62 |

**Nissan Chemical Industries, Ltd., 1985d.** This second feeding study in beagle dogs was conducted over a 52 week period at the same levels of exposure as in the previous study (Nippon Experimental Research Institute, 1982). Six male and six female dogs per dose level were administered 0 ppm (controls), 25 ppm, 100 ppm or 400 pmm quizalofop-ethyl in diet. The experimental design was essentially the same as the previous study, with the exception that a ground diet was used rather than a pelleted diet. Insufficient information is provided in the two study reports to allow comparison of the dietary composition in the two studies.

One female in the 100 ppm group died during the course of the study, apparently from an ulcer in the ileum. The death was not considered to be treatment related. All other animals were sacrificed at the end of the experimental period, and all animals were necropsied (although data from animals that died prematurely are not provided). Organs were harvested from all animals in this study, including those that died during the treatment period. Mean ovary weights were reported, and are summarized in Table C.2.2.3. Total ovary weights were similar in control, 25 ppm and 100 ppm groups, but were somewhat lower in the 400 ppm group. No statistical analysis appears to have been performed on these data by the study authors.

Table C.2.2.3. Ovary Weights from Dogs Exposed to Quizalofop-Ethyl in Diet for 52 Weeks (Nissan Chemical Industries, Ltd., 1985d).

| Treatment Group | N | Left Ovaries (g) Mean ± S.D. (organ/body weight ratio, %) | Right Ovaries (g) Mean ± S.D. (organ/body weight ratio, %) | Total (g) Mean ± S.D. (organ/body weight ratio, %) |
|---|---|---|---|---|
| 0 ppm | 6 | 0.801 ± 0.352 (0.007 ± 0.003) | 0.624 ± 0.213 (0.005 ± 0.002) | 1.421 ± 0.365 (0.012 ± 0.003) |
| 25 ppm | 6 | 0.745 ± 0. 366 (0.007 ± 0.003) | 0.686 ± 0.259 (0.006 ± 0.002) | 1.431 ± 0.559 (0.013 ± 0.004) |
| 100 ppm | 6 | 0.705 ± 0.367 (0.006 ± 0.003) | 0.721 ± 0.322 (0.007 ± 0.003) | 1.426 ± 0.677 (0.013 ± 0.006) |
| 400 ppm | 6 | 0.583 ± 0. 088 (0.005 ± 0.001) | 0.603 ± 0.106 (0.005 ± 0.001) | 1.186 ± 0.164 (0.011 ± 0.001) |

Tissues and organs that were used for histopathology were preserved in 10% buffered formalin. The results of histological examinations were reported only when pathological findings occurred; histopathological findings for female reproductive organs are summarized in Table C.2.2.4. None of these pathological findings appeared to be treatment related. Food and water consumption were reported to have been unaffected by treatment, and there were no treatment-related changes in clinical condition or behavior. The authors of the study report considered the highest dose tested, 400 ppm, to be a no effect level.

Table C.2.2.4. Results of Histopathological Examination of Ovary, Uterus and Mammary Gland from Dogs Exposed to Quizalofop-Ethyl in Diet for 52 Weeks (Nissan Chemical Industries, Ltd., 1985d)

| | | Treatment Group | | | |
|---|---|---|---|---|---|
| Organ | Findings | 0 ppm (control) (n=6) | 25 ppm (n=6) | 100 ppm (n=5) | 400 ppm (n=6) |
| Ovary | Enlarged | 1 | 0 | 0 | 0 |
| | Corpora lutea | 1 | 0 | 0 | 0 |
| Uterus | Distension | 0 | 0 | 0 | 1 |
| Mammary gland | Acinar hyperplasia | 0 | 1 | 0 | 0 |

**Nissan Chemical Industries, Ltd., 1982.** Male and female Sprague-Dawley rats were administered 0 (control), 40, 128 or 1280 ppm quizalofop-ethyl in diet for a period of 13 weeks, beginning when the animals were approximately five weeks of age. These dietary concentrations corresponded to average intakes of 0, 3.0, 9.7 and 93.6 mg/kg/day by females over the 13 week exposure period. Animals were randomly distributed among treatment groups, with 20 males and 20 females/group. Fifteen animals of each sex/group were scheduled for sacrifice at the end of the exposure period, while the remaining five animals were allowed a six week recovery period before sacrifice.

Animals had free access to tap water and diet. Clinical observations were made daily for each animal during the first four weeks of treatment, then weekly thereafter. Food intake was measured weekly on the basis of total intake/cage (five animals/cage), and water intake was measured on a daily basis during weeks five and 10 of treatment. Individual animals were weighed weekly. Urine samples were collected from 10 females/group during weeks three and 11 of treatment, and blood samples were taken from 10 lightly-anesthetized females per group on weeks four and 12 of treatment.

Three females scheduled for sacrifice at the end of the treatment period died during treatment, one from each of the 40, 128 and 1280 ppm groups. One female from the 128 ppm group died during the recovery period. The deaths of three of these animals were attributed to overexposure to anesthetic during blood sampling. The death of the

remaining animal, which died during treatment with 128 ppm quizalofop-ethyl, was unaccounted for, other than a notation that the animal was found dead in week 4 of treatment after having exhibited no prior signs of ill health. No clinical findings were noted during the course of the study that were considered to be treatment-related, and the behavior and appearance of the treated animals was reported to be the same as that of the controls.

There appeared to be no significant affects on uterine or ovarian weights in any of the treatment groups, either at the end of the 13 week treatment period or the six week recovery period (Table C.2.2.5). Macroscopic examination of female reproductive organs at the end of the treatment period revealed bilateral fluid distension of the uterine horns in 1/14 females in the 40 ppm group and 1/14 females in the 1280 ppm group, fluid distension of the peri-ovarian sac in 1/14 females in the 128 ppm group and absence of corpora lutea in the ovaries of 1/14 females in the 1280 ppm group. No other abnormal observations were reported. At the end of the six week recovery period, 1/4 females in the 128 ppm group had fluid distension of the uterus. Tissues and organs that were used for histopathology were preserved in 10% buffered formalin. No abnormalities of female reproductive organs were reported for any animals on the basis of microscopic examination.

Table C.2.2.5. Uterus and Ovary Weights from Rats Exposed to Quizalofop-Ethyl in Diet for 13 Weeks (Nissan Chemical Industries, Ltd., 1982)

| Treatment Group | Uterus Weight (g) at End of 13 Week Treatment Mean ± S.D. (n) | Uterus Weight (g) After 6 Week Recovery Mean ± S.D. (n) | Ovary Weight (mg) at End of 13 Week Treatment Mean ± S.D. (n) | Ovary Weight (mg) After 6 Week Recovery Mean ± S.D. (n) |
|---|---|---|---|---|
| 0 ppm | 0.49 ± 0.096 (15) | 0.62 ± 0.217 (5) | 76 ± 15.7 (15) | 65 ± 10.8 (5) |
| 40 ppm | 0.54 ± 0.156 (14) | 0.54 ± 0.055 (5) | 66 ± 11.5 (14) | 69 ± 13.7 (5) |
| 128 ppm | 0.52± 0.105 (14) | 0.70 ± 0.400 (4) | 75 ± 23.1 (14) | 66 ± 13.1 (4) |
| 1280 ppm | 0.53 ± 0.114 (14) | 0.54 ± 0.089 (5) | 70 ± 16.8 (14) | 57 ± 7.4 (5) |

**Nissan Chemical Industries, Ltd., 1985e.** Male and female Sprague-Dawley rats were administered 0 (control), 25, 100 or 400 ppm quizalofop-ethyl in diet for a period of 104 weeks for males and 105 weeks for females, beginning when the animals were approximately five weeks of age. These dietary concentrations corresponded to average intakes of 0, 1.1, 4.6 and 18.6 mg/kg/day by females over the treatment period. Animals were randomly distributed among treatment groups, with 50 males and 50 females/group. Satellite groups of 35 animals of each sex were maintained at each exposure level, and were sacrificed at interim timepoints. Ten males and 10 females were sacrificed after 26 weeks of treatment, and 10 more animals of each sex after 52 weeks of treatment. The remaining satellite animals were killed after 78 weeks of treatment.

Animals had free access to tap water and diet. Clinical observations were made daily for each animal during the first four weeks of treatment, then weekly thereafter. Food intake was measured weekly on the basis of total intake/cage (5 animals/cage), and water intake was measured on a daily basis during weeks 11 and 24 of treatment. Individual animals were weighed weekly.

There were no clinical observations made during the treatment period that were considered to reflect treatment-related changes. Food and water intakes did not differ significantly between control and any treatment groups. Mortality across the treatment period is summarized in Table C.2.2.6. There were no significant differences in mortality between control and any treatment groups.

Table C.2.2.6. Mortality in Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| Number of Deaths during Weeks (%) | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 1-26 | 0/50 (0) | 0/50 (0) | 0/50 (0) | 0/50 (0) |
| 27-52 | 3/50 (6) | 2/50 (4) | 1/50 (2) | 0/50 (0) |
| 53-78 | 7/47 (15) | 11/48 (23) | 2/49 (4) | 5/50 (10) |
| 79-106 | 17/40 (43) | 16/37 (43) | 19/47 (40) | 16/45 (36) |
| 1-106 | 27/50 (54) | 29/50 (58) | 22/50 (44) | 21/50 (42) |

Weight gain over the periods from 0-78 and 0-105 weeks of treatment is summarized in Table C.2.2.7. There were no significant differences in weight gain among females of any groups group over the first 78 weeks of treatment or over the entire treatment period.

Table C.2.2.7. Weight Gain in Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| Mean Weight Gain (g) Between Weeks | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 0-78 | 383 | 405 | 421 | 394 |
| 0-105 | 417 | 431 | 445 | 407 |

Table C.2.2.8. Macroscopic Pathology Examination of Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Found dead or sacrificed *in extremis* | n=1 | n=2 | n=2 | n=2 |
| Ovary/ies | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Multiple nodules | 0 | 0 | 0 | 0 |
| Cyst/s | 0 | 0 | 0 | 0 |
| No corpora lutea visible | 0 | 0 | 0 | 0 |
| Uterus | | | | |
| Mass/es | 0 | 0 | 0 | 0 |
| Nodule | 0 | 0 | 0 | 0 |
| Fluid swelling/s | 0 | 0 | 0 | 1 |
| 26 Week Interim Sacrifice | n=10 | n=10 | n=10 | n=10 |
| Ovary/ies | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Multiple nodules | 0 | 0 | 0 | 0 |
| Cyst/s | 2 | 0 | 0 | 0 |
| No corpora lutea visible | 0 | 0 | 0 | 0 |
| Uterus | | | | |
| Mass/es | 0 | 0 | 0 | 0 |
| Nodule | 0 | 0 | 0 | 0 |
| Fluid swelling/s | 0 | 0 | 0 | 0 |
| 52 Week Interim Sacrifice | n=10 | n=10 | n=10 | n=10 |
| Ovary/ies | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Multiple nodules | 0 | 0 | 0 | 0 |
| Cyst/s | 0 | 0 | 0 | 0 |
| No corpora lutea visible | 5 | 4 | 7 | 7 |
| Uterus | | | | |
| Mass/es | 0 | 0 | 0 | 0 |
| Nodule | 0 | 0 | 0 | 0 |
| Fluid swelling/s | 0 | 0 | 0 | 0 |
| 78Week Interim Sacrifice | n=13 | n=14 | n=12 | n=11 |
| Ovary/ies | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Multiple nodules | 0 | 0 | 0 | 0 |
| Cyst/s | 3 | 1 | 2 | 1 |
| No corpora lutea visible | 5 | 1 | 1 | 1 |
| Uterus | | | | |
| Mass/es | 1 | 0 | 1 | 0 |
| Nodule | 0 | 0 | 0 | 0 |
| Fluid swelling/s | 2 | 1 | 0 | 0 |

Table C.2.2.8. Macroscopic Pathology Examination of Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued).

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Terminal Sacrifice | n=23 | n=21 | n=28 | n=29 |
| Ovary/ies | | | | |
| Mass | 0 | 0 | 1 | 0 |
| Multiple nodules | 0 | 0 | 0 | 0 |
| Cyst/s | 6 | 1 | 8 | 9 |
| No corpora lutea visible | 9 | 7 | 11 | 13 |
| Uterus | | | | |
| Mass/es | 3 | 1 | 1 | 4 |
| Nodule | 0 | 0 | 0 | 0 |
| Fluid swelling/s | 2 | 3 | 3 | 5 |
| Found dead or sacrificed *in extremis* (between weeks 78 and 105) | n=27 | n=29 | n=22 | n=21 |
| Ovary/ies | | | | |
| Mass | 1 | 0 | 0 | 0 |
| Multiple nodules | 1 | 0 | 0 | 0 |
| Cyst/s | 4 | 1 | 3 | 4 |
| No corpora lutea visible | 4 | 4 | 6 | 4 |
| Uterus | | | | |
| Mass/es | 0 | 4 | 0 | 3 |
| Nodule | 0 | 1 | 0 | 0 |
| Fluid swelling/s | 1 | 2 | 0 | 0 |

The results of macroscopic examination of reproductive organs are summarized in Table C.2.2.8, organ weights (reproductive organs and any other organs where significant effects were observed) are summarized in Table C.2.2.9 and results of histopathology of the reproductive organs are summarized in Table C.2.2.10. Tissues and organs that were used for histopathology were preserved in 10% neutral buffered formalin. Uterus weights were lower in all of the treatment groups than in controls at 26, 52 and 78 week interim sacrifices, but only in the 25 and 100 ppm groups at terminal sacrifice (78 weeks). Although the effects on uterus weights at 26 and 78 weeks were statistically significant, they were considered by the study authors to be of no toxicological importance. Liver weight was consistently reduced in the 400 ppm animals at all timepoints, while only sporadic effects were observed on other organs

Table C.2.2.9. Organ Weights from Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 26 Week Interim Sacrifice | | | | |
| Mean Uterus Weight (g) | 0.80 | 0.62* | 0.57* | 0.61* |
| Mean Ovaries Weight (mg) | 143 | 57 | 71 | 66 |
| Mean Liver Weight (g) | 11.5 (11.1) | 11.3 (11.0) | 12.1 (12.3) | 13.1**(13.7) |
| Mean Spleen Weight (g) | 0.58 (0.56) | 0.53 (0.52) | 0.49*(0.50) | 0.49*(0.52) |
| 52 Week Interim Sacrifice | | | | |
| Mean Uterus Weight (g) | 1.05 | 0.73 | 0.94 | 0.93 |
| Mean Ovaries Weight (mg) | 67 | 77 | 62 | 57 |
| Mean Liver Weight (g) | 16.7 (15.7) | 16.3 (16.9) | 15.9 (16.5) | 20.6**(20.6) |
| Mean Spleen Weight (g) | 0.58 (0.56) | 0.55 (0.56) | 0.58 (0.59) | 0.61 (0.61) |
| 78Week Interim Sacrifice | | | | |
| Mean Uterus Weight (g) | 1.14 | 0.85* | 0.86* | 0.81** |
| Mean Ovaries Weight (mg) | 66 | 66 | 69 | 69 |
| Mean Liver Weight (g) | 17.6 (18.0) | 17.1 (17.2) | 19.4 (20.7) | 20.9**(20.9) |
| Mean Spleen Weight (g) | 0.74 (0.73) | 0.77 (0.76) | 0.68 (0.70) | 0.67 (0.66) |
| Terminal Sacrifice (Week 104/105) | | | | |
| Mean Uterus Weight (g) | 0.89 (0.95) | 0.75 (0.80) | 0.79 (0.82) | 0.98 (1.11) |
| Mean Ovaries Weight (mg) | 75 (95) | 71 (77) | 80 (90) | 79 (86) |
| Mean Liver Weight (g) | 20.1 (20.0) | 20.0 (20.1) | 21.6 (22.2) | 24.2**(23.7) |
| Mean Spleen Weight (g) | 0.85 | 0.75 | 1.01 | 0.71 |

** p<0.05 ** p<0.01 (Williams' test), compared to control value*
*Where organ weights were adjusted for bodyweight as a covariate during statistical analysis, the unadjusted mean is shown in parentheses.*

Table C.2.2.10. Histopathology Examination of Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 26 Week Interim Sacrifice | | | | |
| Uterus | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 10 | 10 | 10 | 10 |
| Squamous metaplasia of endometrial glands | 0 | 0 | 0 | 0 |
| Dilated endometrial glands | 0 | 0 | 0 | 0 |
| Cystic endometrial gland(s) | 0 | 0 | 0 | 0 |
| Endometrial polyp | 0 | 0 | 0 | 0 |
| Dilated lumen | 0 | 0 | 0 | 0 |
| Endometritis | 0 | 0 | 0 | 0 |
| Cervix | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 10 | 10 | 10 | 9 |
| Keratin cyst | 0 | 0 | 0 | 1 |
| Diffuse fibromatosis | 0 | 0 | 0 | 0 |
| Ovaries | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 0 | 0 | 0 | 0 |
| Cyst(s) | 0 | 0 | 0 | 0 |
| Haemorrhagic cyst | 0 | 0 | 0 | 0 |
| No corpora lutea | 0 | 0 | 0 | 0 |
| 52 Week Interim Sacrifice | | | | |
| Uterus | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 6 | 7 | 5 | 6 |
| Squamous metaplasia of endometrial glands | 4 | 3 | 3 | 4 |
| Dilated endometrial glands | 1 | 0 | 0 | 0 |
| Cystic endometrial gland(s) | 0 | 0 | 2 | 0 |
| Endometrial polyp | 0 | 0 | 0 | 0 |
| Dilated lumen | 0 | 0 | 0 | 0 |
| Endometritis | 0 | 0 | 0 | 0 |
| Cervix | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 10 | 10 | 10 | 10 |
| Keratin cyst | 0 | 0 | 0 | 0 |
| Diffuse fibromatosis | 0 | 0 | 0 | 0 |
| Ovaries | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 5 | 6 | 2 | 1 |
| Cyst(s) | 0 | 0 | 1 | 0 |
| Haemorrhagic cyst | 0 | 0 | 0 | 0 |
| No corpora lutea | 5 | 4 | 8 | 9 |

Table C.2.2.10. Histopathology Examination of Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 78Week Interim Sacrifice | | | | |
| Uterus | n=14 | n=13 | n=13 | n=13 |
| Not remarkable | 7 | 7 | 7 | 7 |
| Squamous metaplasia of endometrial glands | 2 | 5 | 4 | 3 |
| Dilated endometrial glands | 0 | 0 | 0 | 0 |
| Cystic endometrial gland(s) | 5 | 5 | 2 | 5 |
| Endometrial polyp | 2 | 0 | 1 | 0 |
| Dilated lumen | 1 | 0 | 0 | 0 |
| Endometritis | 1 | 0 | 0 | 0 |
| Cervix | n=14 | n=13 | n=13 | n=13 |
| Not remarkable | 14 | 13 | 12 | 12 |
| Keratin cyst | 0 | 0 | 0 | 0 |
| Diffuse fibromatosis | 0 | 0 | 1 | 0 |
| Ovaries | n=14 | n=13 | n=13 | n=13 |
| Not remarkable | 7 | 6 | 3 | 8 |
| Cyst(s) | 1 | 1 | 2 | 1 |
| Haemorrhagic cyst | 0 | 0 | 0 | 0 |
| No corpora lutea | 7 | 6 | 8 | 4 |

Table C.2.2.10. Histopathology Examination of Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Terminal Sacrifice (105 Weeks) | | | | |
| Uterus | n=23 | n=20 | n=28 | n=29 |
| Not remarkable | 12 | 17 | 19 | 15 |
| Autolysis | 0 | 0 | 0 | 0 |
| Prolapse | 0 | 0 | 0 | 1 |
| Mesometrial necrosis/haemorrhage | 0 | 0 | 0 | 0 |
| Squamous metaplasia of endometrial glands | 3 | 1 | 3 | 2 |
| Dilated endometrial glands | 0 | 0 | 0 | 0 |
| Cystic endometrial gland(s) | 5 | 3 | 4 | 9 |
| Endometrial polyp | 3 | 1 | 1 | 1 |
| Dilated lumen | 2 | 2 | 2 | 5 |
| Endometritis | 0 | 0 | 0 | 0 |
| Keratin in lumen | 0 | 0 | 0 | 0 |
| Cystic/hyperplastic endometrial glands | 2 | 0 | 0 | 0 |
| Prolapsed endometrial polyp | 0 | 0 | 0 | 1 |
| Endometrial polyp with squamous metaplasia | 0 | 0 | 0 | 1 |
| Polyp | 0 | 0 | 0 | 1 |
| Hyperplasia of endometrial gland | 0 | 0 | 1 | 0 |
| Cervix | n=23 | n=21 | n=28 | n=29 |
| Not remarkable | 18 | 13 | 19 | 20 |
| Keratin cyst | 0 | 0 | 1 | 0 |
| Diffuse fibromatosis | 0 | 1 | 0 | 1 |
| Invasion by uterine tumour | 0 | 0 | 0 | 0 |
| Epithelial mucification | 5 | 7 | 7 | 6 |
| Hypertrophic fibrosis | 0 | 0 | 0 | 0 |
| Cervicitis | 0 | 0 | 0 | 0 |
| Medial Degeneration/periarteritis | 0 | 1 | 0 | 0 |
| Containing prolapsed uterine endometrial polyp | 0 | 0 | 0 | 1 |
| Fibrous polyp | 0 | 0 | 0 | 1 |
| Epithelial hyperplasia | 0 | 0 | 1 | 0 |
| Smooth muscle hyperplasia | 0 | 0 | 1 | 0 |
| Ovaries | n=23 | n=21 | n=28 | n=29 |
| Not remarkable | 5 | 9 | 9 | 5 |
| Autolysis | 0 | 0 | 0 | 0 |
| Cyst(s) | 6 | 0 | 4 | 7 |
| No corpora lutea | 11 | 7 | 13 | 16 |
| Tubular hyperplasia | 7 | 11 | 11 | 15 |
| Cystic bursa | 0 | 0 | 0 | 0 |

Table C.2.2.10. Histopathology Examination of Female Rats Exposed to Quizalofop-Ethyl in Diet for 105 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Found dead or sacrificed *in extremis* | | | | |
| Uterus | n=27 | n=29 | n=21 | n=21 |
| Not remarkable | 22 | 12 | 15 | 14 |
| Autolysis | 0 | 2 | 1 | 0 |
| Prolapse | 0 | 1 | 0 | 0 |
| Mesometrial necrosis/haemorrhage | 0 | 1 | 0 | 0 |
| Squamous metaplasia of endometrial glands | 2 | 3 | 2 | 1 |
| Dilated endometrial glands | 0 | 2 | 0 | 1 |
| Cystic endometrial gland(s) | 4 | 7 | 1 | 2 |
| Endometrial polyp | 0 | 2 | 2 | 2 |
| Dilated lumen | 0 | 1 | 0 | 0 |
| Endometritis | 0 | 0 | 0 | 1 |
| Keratin in lumen | 0 | 1 | 0 | 0 |
| Cystic/hyperplastic endometrial glands | 0 | 0 | 0 | 0 |
| Prolapsed endometrial polyp | 0 | 0 | 0 | 0 |
| Endometrial polyp with squamous metaplasia | 0 | 0 | 0 | 0 |
| Polyp | 0 | 0 | 0 | 0 |
| Hyperplasia of endometrial gland | 0 | 0 | 0 | 0 |
| Cervix | n=27 | n=29 | n=21 | n=21 |
| Not remarkable | 21 | 25 | 18 | 15 |
| Keratin cyst | 0 | 0 | 0 | 0 |
| Diffuse fibromatosis | 0 | 0 | 0 | 1 |
| Invasion by uterine tumour | 0 | 0 | 1 | 0 |
| Epithelial mucification | 5 | 2 | 1 | 4 |
| Hypertrophic fibrosis | 1 | 0 | 0 | 0 |
| Cervicitis | 0 | 0 | 1 | 0 |
| Medial Degeneration/periarteritis | 0 | 0 | 0 | 0 |
| Containing prolapsed uterine endometrial polyp | 0 | 0 | 0 | 0 |
| Fibrous polyp | 0 | 0 | 0 | 0 |
| Epithelial hyperplasia | 0 | 0 | 0 | 0 |
| Smooth muscle hyperplasia | 0 | 0 | 0 | 0 |
| Ovaries | n=27 | n=29 | n=22 | n=21 |
| Not remarkable | 13 | 12 | 10 | 10 |
| Autolysis | 0 | 2 | 0 | 0 |
| Cyst(s) | 4 | 1 | 2 | 3 |
| No corpora lutea | 6 | 12 | 10 | 7 |
| Tubular hyperplasia | 5 | 4 | 1 | 3 |
| Cystic bursa | 1 | 0 | 0 | 0 |

**Nissan Chemical Industries, Ltd., 1985f**. Male and female CD-1 mice were administered 0 (control), 2, 10, 80 or 320 ppm quizalofop-ethyl in diet for a period of 78 weeks, beginning when the animals were approximately six and a half weeks of age. (The 10 and 320 ppm concentrations were reported to correspond to 1.88 and 58.47 mg/kg/day, respectively, for female mice; intake levels corresponding to other dietary concentrations were not reported). Animals were randomly distributed among treatment groups, with 50 males and 50 females per group. Two satellite groups (A and B) of 10 animals of each sex per group were maintained at each exposure level, and all surviving animals in these groups were sacrificed at interim timepoints. The surviving animals in satellite group A were sacrificed after 26 weeks of treatment and the surviving animals of satellite group B after 52 weeks of treatment. The animals of the main treatment groups were killed after 78 weeks of treatment.

Clinical observations were made weekly during weeks 1-14 of treatment, and biweekly thereafter. Food consumption was recorded weekly during weeks 1-14 of treatment, and biweekly thereafter. Water intake does not appear to have been measured in this study. Individual animals were weighed weekly during weeks 1-14 of treatment, and biweekly thereafter.

Mortality during the course of treatment in female mice is summarized in Table C.2.2.11. Sacrifice of moribund animals is included, but accidental deaths that were not treatment related are not, nor are scheduled sacrifices. Total mortality across 0, 2, 10, 80 and 320 ppm groups was 16, 12, 15, 19 and 23 deaths, respectively. It was reported that there were no significant differences in survival rates between any of the treatment groups and controls.

There were no obvious treatment-related effects on incidence of clinical signs, other than an possible increase in the incidence of swollen abdomens in the high-dose group (8, 8, 9, 10 and 17 cases in the 0, 2, 10, 80 and 320 ppm group females, respectively).

Table C.2.2.11. Mortality in Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| Number of Deaths during Weeks (%) | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 0-5 | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 1/70 (1.4) | 0 | 0 |
| 7-13 | 0 | 0 | 0 | 0 | 0 |
| 14 | 0 | 0 | 1/70 (1.4) | 0 | 0 |
| 15 | 0 | 0 | 1/70 (1.4) | 0 | 0 |
| 16-18 | 0 | 0 | 0 | 0 | 0 |
| 19 | 0 | 0 | 0 | 1/70 (1.4) | 0 |
| 20-24 | 0 | 0 | 0 | 0 | 0 |
| 25 | 1/70 (1.4) | 0 | 0 | 1/70 (1.4) | 0 |
| 26-27 | 0 | 0 | 0 | 0 | 0 |
| 28 | 0 | 0 | 0 | 0 | 1/60 (1.7) |
| 29 | 0 | 0 | 0 | 1/60 (1.7) | 0 |
| 30-32 | 0 | 0 | 0 | 0 | 0 |
| 33 | 1/61 (1.6) | 0 | 0 | 0 | 0 |
| 34 | 0 | 0 | 0 | 0 | 0 |
| 35 | 0 | 0 | 0 | 1/60 (1.7) | 1/60 (1.7) |
| 36-39 | 0 | 0 | 0 | 0 | 0 |
| 40 | 0 | 0 | 0 | 1/60 (1.7) | 0 |
| 41-44 | 0 | 0 | 0 | 0 | 0 |
| 45 | 1/61 (1.6) | 0 | 0 | 0 | 0 |
| 46 | 0 | 0 | 0 | 1/60 (1.7) | 0 |
| 47 | 0 | 1/60 (1.7) | 0 | 0 | 0 |
| 48 | 0 | 0 | 0 | 1/60 (1.7) | 0 |
| 49 | 0 | 0 | 1/58 (1.7) | 1/60 (1.7) | 1/61 (1.6) |
| 50-51 | 0 | 0 | 0 | 0 | 0 |
| 52 | 0 | 0 | 1/58 (1.7) | 1/60 (1.7) | 0 |
| 53 | 0 | 1/60 (1.7) | 0 | 0 | 0 |
| 54 | 0 | 0 | 0 | 0 | 1/51 (2.0) |
| 55 | 0 | 0 | 0 | 0 | 0 |
| 56 | 0 | 0 | 0 | 0 | 1/51 (2.0) |
| 57 | 0 | 0 | 0 | 0 | 0 |
| 58 | 0 | 0 | 0 | 1/53 (1.9) | 0 |
| 59 | 0 | 0 | 0 | 0 | 1/51 (2.0) |
| 60 | 0 | 1/51 (2.0) | 0 | 0 | 0 |
| 61 | 0 | 0 | 0 | 0 | 0 |
| 62 | 1/51 (2.0) | 0 | 1/48 (2.1) | 0 | 0 |
| 63 | 0 | 0 | 0 | 1/53 (1.9) | 2/51 (3.9) |

Table C.2.2.11. Mortality in Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| Number of Deaths during Weeks (%) | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 64 | 0 | 0 | 1/48 (2.1) | 0 | 0 |
| 65 | 1/51 (2.0) | 0 | 0 | 0 | 1/51 (2.0) |
| 66 | 0 | 1/51 (2.0) | 0 | 0 | 1/51 (2.0) |
| 67 | 0 | 2/51 (3.9) | 1/48 (2.1) | 0 | 2/51 (3.9) |
| 68 | 1/51 (2.0) | 0 | 0 | 0 | 0 |
| 69 | 0 | 0 | 1/48 (2.1) | 1/53 (1.9) | 0 |
| 70 | 0 | 0 | 1/48 (2.1) | 3/53 (5.7) | 0 |
| 71 | 0 | 1/51 (2.0) | 0 | 1/53 (1.9) | 3/51 (5.9) |
| 72 | 2/51 (3.9) | 1/51 (2.0) | 2/48 (4.2) | 1/53 (1.9) | 1/51 (2.0) |
| 73 | 0 | 0 | 0 | 0 | 1/51 (2.0) |
| 74 | 0 | 0 | 0 | 0 | 1/51 (2.0) |
| 75 | 2/51 (3.9) | 2/51 (3.9) | 0 | 1/53 (1.9) | 0 |
| 76 | 2/51 (3.9) | 0 | 0 | 0 | 1/51 (2.0) |
| 77 | 2/51 (3.9) | 1/51 (2.0) | 1/48 (2.1) | 0 | 0 |
| 78 | 0 | 1/51 (2.0) | 2/48 (4.2) | 1/53 (1.9) | 1/51 (2.0) |
| 79 | 2/51 (3.9) | 0 | 0 | 0 | 2/51 (3.9) |
| 80 | 0 | 0 | 0 | 0 | 1/51 (2.0) |
| Total deaths/group | 16 | 12 | 15 | 19 | 23 |

It was reported that body weights across groups were homogeneous at the time of random assignment of animals to groups; however, when treatment began four days after assignment of animals to groups, body weights in the 10 and 320 ppm groups were significantly below control values and may have influenced subsequent growth analysis. There was no apparent treatment-related effect on body weights or weight gain between treatment groups and controls. The 10 and 320 groups were slightly but significantly heavier than the control groups at several timepoints but, as noted above, this may have been attributable to the slightly lower bodyweight of these animals at the beginning of treatment. The 80 ppm group was also significantly heavier than the control group at several timepoints, however. Food consumption was also not consistently affected by treatment with quizalofop-ethyl. The only statistically significant differences were lower food intake by the 10 ppm group than controls in weeks 8 and 12 of treatment.

Table C.2.2.12. Gross Pathological Examination of Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | | | | | |
| Ovaries | n=9 | n=10 | n=9 | n=10 | n=9 |
| Not remarkable | 7 | 9 | 6 | 4 | 7 |
| Cyst(s) | 2 | 1 | 3 | 4 | 2 |
| Dark | 0 | 0 | 0 | 1 | 0 |
| Nodular | 0 | 0 | 0 | 1 | 0 |
| Uterus | n=9 | n=10 | n=9 | n=10 | n=9 |
| Not remarkable | 3 | 1 | 4 | 4 | 3 |
| Cyst(s) | 2 | 6 | 5 | 5 | 5 |
| Distended | 1 | 3 | 1 | 0 | 0 |
| Intraluminal fluid | 2 | 1 | 0 | 0 | 0 |
| Thickened wall(s) | 3 | 4 | 1 | 3 | 4 |
| Liver | n=9 | n=10 | n=9 | n=10 | n=9 |
| Not remarkable | 6 | 10 | 9 | 10 | 8 |
| Dark | 0 | 0 | 0 | 0 | 0 |
| Enlarged | 0 | 0 | 0 | 0 | 0 |
| Friable | 0 | 0 | 0 | 0 | 0 |
| Pale | 1 | 0 | 0 | 0 | 0 |
| Pale focus (I)/area(s) | 0 | 0 | 0 | 0 | 1 |
| Dark focus (I)/area(s) | 0 | 0 | 0 | 0 | 0 |
| H- Dark focus (I)/area(s) | 2 | 0 | 0 | 0 | 0 |
| 52 Week Interim Sacrifice | | | | | |
| Ovaries | n=10 | n=9 | n=10 | n=7 | n=10 |
| Not remarkable | 6 | 3 | 7 | 5 | 5 |
| Cyst(s) | 4 | 6 | 3 | 2 | 5 |
| Uterus | n=10 | n=9 | n=10 | n=7 | n=10 |
| Not remarkable | 1 | 0 | 1 | 3 | 2 |
| Cyst(s) | 7 | 6 | 5 | 3 | 7 |
| Distended | 2 | 1 | 5 | 2 | 1 |
| Intraluminal fluid | 0 | 1 | 0 | 0 | 0 |
| Thickened wall(s) | 7 | 4 | 4 | 1 | 3 |
| Small mass(es) | 1 | 0 | 0 | 0 | 0 |
| H-thickened | 0 | 1 | 0 | 0 | 0 |

Table C.2.2.12. Gross Pathological Examination of Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| Liver | n=10 | n=9 | n=10 | n=7 | n=10 |
| Not remarkable | 8 | 9 | 8 | 4 | 1 |
| Dark | 0 | 0 | 0 | 2 | 6 |
| Prominent vessels | 0 | 0 | 1 | 0 | 0 |
| Enlarged | 1 | 0 | 2 | 1 | 6 |
| Pale focus (I)/area(s) | 1 | 0 | 0 | 0 | 0 |
| Dark focus (I)/area(s) | 0 | 0 | 1 | 0 | 0 |
| Mottled | 0 | 0 | 0 | 0 | 0 |
| Raised area(s) | 0 | 0 | 0 | 0 | 0 |
| Small mass(es) | 0 | 0 | 0 | 0 | 1 |
| Irregularly shaped | 1 | 0 | 0 | 0 | 1 |
| Firm | 1 | 0 | 0 | 0 | 0 |
| H-irregularly shaped | 1 | 0 | 0 | 0 | 0 |
| Terminal Sacrifice | | | | | |
| Ovaries | n=35 | n=39 | n=33 | n=34 | n=28 |
| Not remarkable | 18 | 13 | 12 | 11 | 9 |
| Cyst(s) | 17 | 22 | 19 | 23 | 17 |
| Nodular | 0 | 0 | 1 | 0 | 0 |
| Small mass(es) | 0 | 1 | 0 | 0 | 1 |
| Unequal size | 0 | 0 | 1 | 0 | 0 |
| Firm (hard) | 0 | 1 | 0 | 0 | 0 |
| Enlarged | 0 | 4 | 1 | 0 | 1 |
| Pale | 0 | 0 | 1 | 0 | 0 |
| Dark focus (I)/area(s) | 1 | 0 | 0 | 0 | 0 |
| Uterus | n=35 | n=39 | n=33 | n=34 | n=28 |
| Not remarkable | 11 | 14 | 4 | 7 | 10 |
| Cyst(s) | 17 | 17 | 26 | 25 | 16 |
| Distended | 0 | 3 | 1 | 1 | 0 |
| Intraluminal fluid | 0 | 0 | 0 | 0 | 1 |
| Thickened wall(s) | 10 | 11 | 15 | 8 | 3 |
| Mass(es) | 1 | 1 | 1 | 0 | 0 |
| Small mass(es) | 2 | 0 | 0 | 3 | 0 |
| Dark | 0 | 0 | 1 | 0 | 0 |
| Polyp(s) | 0 | 1 | 0 | 0 | 1 |
| Raised area(s) | 0 | 0 | 0 | 1 | 0 |
| H-small mass(es) | 0 | 0 | 1 | 0 | 0 |

Table C.2.2.12. Gross Pathological Examination of Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| Liver | n=35 | n=39 | n=33 | n=34 | n=28 |
| Not remarkable | 31 | 33 | 26 | 25 | 1 |
| Dark | 0 | 1 | 2 | 5 | 26 |
| Enlarged | 0 | 2 | 0 | 2 | 11 |
| Pale | 0 | 0 | 0 | 1 | 0 |
| Pale focus (I)/area(s) | 1 | 3 | 3 | 2 | 2 |
| Dark focus (I)/area(s) | 1 | 1 | 0 | 0 | 0 |
| Mottled | 0 | 0 | 0 | 0 | 0 |
| Raised area(s) | 0 | 0 | 0 | 0 | 0 |
| Small mass(es) | 1 | 0 | 1 | 0 | 1 |
| Irregularly shaped | 1 | 0 | 0 | 0 | 1 |
| Mass(es) | 0 | 0 | 0 | 0 | 0 |
| Cyst(s) | 1 | 0 | 0 | 0 | 0 |
| Small | 0 | 0 | 1 | 0 | 0 |
| H-small mass(es) | 0 | 0 | 0 | 0 | 0 |
| H-cyst(s) | 0 | 0 | 0 | 0 | 0 |
| H-pale focus (I)/area(s) | 0 | 0 | 0 | 0 | 1 |
| H-raised area(s) | 1 | 0 | 0 | 0 | 0 |

The results of gross pathological examinations of tissues are summarized in Table C.2.2.12, absolute organ weights are summarized in Table C.2.2.13 and relative organ weights are summarized in Table C.2.2.14 (for reproductive organs and other organs where a significant effect was reported). Absolute and relative ovarian weights were significantly increased over control weights ($p<0.05$) in all treatment groups at terminal sacrifice (78 weeks), although the magnitude of the effect did not show an obvious dose-response relationship. Absolute ovarian weights were also higher in all treatment groups than in controls at interim sacrifices at 26 and 52 weeks, but none of these increases were reported to be statistically significant.

Table C.2.2.13. Absolute Organ Weights for Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | n=10 | n=10 | n=9 | n=9 | n=10 |
| Terminal Body Weight (g) Mean ± S.D. | 26.4±1.8 | 26.0±1.0 | 25.2±2.5 | 25.7±2.5 | 28.0±1.6 |
| Ovarian Weight (g) Mean ± S.D. | 0.028±0.007 | 0.031±0.020 | 0.029±0.007 | 0.038±0.025 | 0.030±0.007 |
| Liver Weight (g) Mean ± S.D. | 1.22±0.12 | 1.16±0.11 | 1.13±0.18 | 1.25±0.19 | 2.01±0.18 |
| Kidneys Weight (g) Mean ± S.D. | 0.39±0.09 | 0.44±0.04 | 0.43±0.05 | 0.45±0.04 | 0.48*±0.07 |
| 52 Week Interim Sacrifice | n=10 | n=9 | n=10 | n=7 | n=10 |
| Terminal Body Weight (g) Mean ± S.D. | 27.9±2.5 | 28.6±1.7 | 28.6±2.6 | 28.6±3.3 | 29.0±2.3 |
| Ovarian Weight (g) Mean ± S.D. | 0.031±0.020 | 0.035±0.017 | 0.036±0.016 | 0.039±0.023 | 0.048±0.027 |
| Liver Weight (g) Mean ± S.D. | 1.23±0.18 | 1.33±0.14 | 1.35±0.31 | 1.51±0.29 | 2.17*±0.39 |
| Kidneys Weight (g) Mean ± S.D. | 0.47±0.06 | 0.48±0.03 | 0.46±0.07 | 0.47±0.08 | 0.54±0.08 |
| Terminal Sacrifice | n=35 | n=39 | n=33 | n=34 | n=28 |
| Terminal Body Weight (g) Mean ± S.D. | 29.5±2.8 | 30.2±3.2 | 28.8±2.7 | 30.6±2.8 | 30.1±2.6 |
| Ovarian Weight (g) Mean ± S.D. | 0.028±0.029 | 0.058*±0.044 | 0.073*±0.091 | 0.061*±0.023 | 0.056*±0.054 |
| Liver Weight (g) Mean ± S.D. | 1.47±0.23 | 1.54±0.32 | 1.40±0.20 | 1.75*±0.28 | 2.45*±0.81 |
| Kidneys Weight (g) Mean ± S.D. | 0.51±0.23 | 0.52±0.08 | 0.51±0.07 | 0.56*±0.07 | 0.58*±0.09 |

** $p<0.05$ (statistical test not specified)*

Table C.2.2.14. Relative Organ Weights for Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks – Organ/Terminal Bodyweight Ratio (%) (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | n=9 | n=10 | n=9 | n=10 | n=9 |
| Ovaries (mean ± S.D.) | 0.106±0.022 | 0.106±0.070 | 0.117±0.036 | 0.149±0.105 | 0.106±0.025 |
| Liver (mean ± S.D.) | 4.608±0.254 | 4.453±0.320 | 4.449±0.286 | 4.844±0.355 | 7.165*±0.403 |
| Kidneys (mean ± S.D.) | 1.461±0.324 | 1.683±0.165 | 1.698*±0.131 | 1.753*±0.117 | 1.710*±0.188 |
| 52 Week Interim Sacrifice | n=10 | n=9 | n=10 | n=7 | n=10 |
| Ovaries (mean ± S.D.) | 0.115±0.085 | 0.123±0.062 | 0.127±0.051 | 0.136±0.077 | 0.162±0.091 |
| Liver (mean ± S.D.) | 4.397±0.436 | 4.657±0.499 | 4.679±0.818 | 5.255*±0.593 | 7.419*±0.893 |
| Kidneys (mean ± S.D.) | 1.670±0.173 | 1.694±0.117 | 1.621±0.170 | 1.623±0.297 | 1.865±0.157 |
| Terminal Sacrifice | n=35 | n=39 | n=33 | n=34 | n=28 |
| Ovaries (mean ± S.D.) | 0.097±0.105 | 0.192*±0.145 | 0.254*±0.145 | 0.198*±0.163 | 0.187*±0.175 |
| Liver (mean ± S.D.) | 4.969±0.622 | 5.077±0.820 | 4.880±0.630 | 5.714*±0.672 | 8.078*±2.443 |
| Kidneys (mean ± S.D.) | 1.743±0.167 | 1.719±0.202 | 1.782±0.266 | 1.846*±0.189 | 1.933±0.231 |

** $p<0.05$ (statistical test not specified)*

Results of histopathological examinations are summarized in Table C.2.2.15. Tissues and organs that were used for histopathology were preserved in 10% neutral buffered formalin.

Table C. 2.2.15. Histopathological Examination of Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | | | | | |
| Ovaries | n=9 | n=10 | n=9 | n=10 | n=9 |
| Not remarkable | 5 | 5 | 4 | 3 | 7 |
| Ovarian cyst(s) | 4 | 4 | 5 | 7 | 2 |
| Paraovarian cysts(s) | 0 | 1 | 1 | 0 | 0 |
| Amyloid | 0 | 0 | 0 | 1 | 0 |
| Hemorrhage | 0 | 1 | 0 | 0 | 0 |
| Uterus | n=9 | n=10 | n=9 | n=10 | n=9 |
| Not remarkable | 0 | 0 | 0 | 0 | 0 |
| Endometrial hyperplasia/cystic endometrial hyperplasia | 8 | 10 | 9 | 10 | 9 |
| Dilation | 2 | 3 | 1 | 2 | 1 |
| Mononuclear infiltration | 0 | 1 | 0 | 0 | 0 |
| Liver | n=9 | n=10 | n=9 | n=10 | n=9 |
| Not remarkable | 1 | 0 | 1 | 2 | 0 |
| B-hepatocellular adenoma | 0 | 0 | 0 | 0 | 0 |
| Diffuse hepatocytic enlargement | 0 | 0 | 0 | 0 | 9 |
| Centrolobular hepatocytic enlargement | 0 | 0 | 0 | 0 | 0 |
| Hepatocytic pigmentation | 0 | 0 | 0 | 1 | 1 |
| Sinusoidal cell pigmentation | 0 | 0 | 0 | 0 | 1 |
| Focal mononuclear infiltration | 6 | 6 | 6 | 5 | 7 |
| Focal hepatitis | 3 | 6 | 4 | 4 | 5 |
| Bile duct hyperplasia | 0 | 0 | 0 | 0 | 0 |
| Coagulative necrosis | 1 | 1 | 0 | 0 | 2 |
| Hepatocytic vacuolization | 1 | 0 | 0 | 1 | 0 |
| Extramedullary hematopoiesis | 3 | 1 | 1 | 1 | 2 |
| Chronic infarct | 1 | 0 | 1 | 0 | 0 |
| Megakaryocytes within sinusoids | 0 | 0 | 1 | 1 | 0 |
| Mineralization | 0 | 0 | 1 | 0 | 0 |

Table C. 2.2.15. Histopathological Examination of Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 52 Week Interim Sacrifice | | | | | |
| Ovaries | n=10 | n=9 | n=10 | n=7 | n=10 |
| Not remarkable | 4 | 3 | 5 | 3 | 1 |
| Ovarian cyst(s) | 4 | 3 | 4 | 3 | 8 |
| Paraovarian cysts(s) | 3 | 2 | 3 | 0 | 2 |
| Amyloid | 0 | 1 | 2 | 1 | 2 |
| Uterus | n=10 | n=9 | n=10 | n=7 | n=10 |
| Not remarkable | 0 | 0 | 0 | 0 | 0 |
| Endometrial hyperplasia/cystic endometrial hyperplasia | 10 | 9 | 10 | 7 | 10 |
| Thrombus (I) | 1 | 0 | 0 | 0 | 0 |
| Amyloid | 0 | 1 | 1 | 0 | 0 |
| Liver | n=10 | n=9 | n=10 | n=7 | n=10 |
| Not remarkable | 0 | 0 | 0 | 0 | 0 |
| B-hepatocellular adenoma | 0 | 0 | 0 | 0 | 0 |
| M-hemangiosarcoma | 0 | 0 | 0 | 0 | 0 |
| Focus (I) of cell alteration | 0 | 0 | 0 | 0 | 0 |
| Diffuse hepatocytic enlargement | 0 | 0 | 0 | 0 | 9 |
| Centrolobular hepatocytic enlargement | 0 | 0 | 0 | 1 | 1 |
| Hepatocytic pigmentation | 0 | 0 | 0 | 3 | 8 |
| Sinusoidal cell pigmentation | 1 | 0 | 3 | 5 | 10 |
| Focal pigmented macrophages | 2 | 5 | 5 | 4 | 10 |
| Amyloid | 0 | 2 | 2 | 1 | 1 |
| Focal mononuclear infiltration | 7 | 6 | 8 | 5 | 8 |
| Focal hepatitis | 6 | 8 | 10 | 7 | 7 |
| Bile duct hyperplasia | 0 | 0 | 0 | 0 | 1 |
| Coagulative necrosis | 0 | 0 | 1 | 0 | 2 |
| Hepatocytic vacuolization | 0 | 0 | 0 | 0 | 0 |
| Extramedullary hematopoiesis | 2 | 0 | 3 | 1 | 0 |
| Chronic infarct | 2 | 0 | 1 | 0 | 1 |
| Hepatocellular cytoplasmic clearing | 0 | 0 | 0 | 0 | 1 |
| Bile duct ectasia | 0 | 0 | 0 | 0 | 0 |
| Fibrosis | 0 | 0 | 0 | 0 | 0 |
| Vascular congestion | 0 | 0 | 1 | 0 | 0 |

Table C. 2.2.15. Histopathological Examination of Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| Terminal Sacrifice | | | | | |
| Ovaries | n=35 | n=39 | n=33 | n=34 | n=28 |
| Not remarkable | 11 | 7 | 5 | 12 | 5 |
| B-granulosa/theca cell tumor | 0 | 0 | 0 | 0 | 1 |
| B-luteoma | 0 | 0 | 1 | 0 | 2 |
| Luteal cell hyperplasia | 0 | 0 | 1 | 0 | 2 |
| X-malignant lymphoma | 0 | 0 | 0 | 0 | 1 |
| Ovarian cyst(s) | 16 | 25 | 20 | 21 | 16 |
| Paraovarian cysts(s) | 4 | 0 | 0 | 0 | 3 |
| Amyloid | 5 | 9 | 8 | 7 | 4 |
| Hemorrhage | 0 | 1 | 2 | 2 | 8 |
| Thrombus (I) | 0 | 0 | 1 | 0 | 1 |
| Mononuclear Infiltration | 0 | 0 | 0 | 1 | 0 |
| Congestion | 0 | 2 | 0 | 0 | 0 |
| Uterus | n=35 | n=39 | n=33 | n=34 | n=28 |
| Not remarkable | 0 | 5 | 2 | 1 | 1 |
| M-leiomyosarcoma | 1 | 0 | 0 | 0 | 0 |
| M-sarcoma arising within an endometrial polyp | 0 | 0 | 0 | 0 | 1 |
| B-leiomyoma | 1 | 2 | 0 | 0 | 0 |
| B-endometrial stromal polyp | 1 | 1 | 2 | 1 | 1 |
| Endometrial hyperplasia/cystic endometrial hyperplasia | 35 | 30 | 31 | 30 | 25 |
| Dilation | 0 | 2 | 0 | 1 | 1 |
| Metritis | 0 | 1 | 0 | 0 | 1 |
| Thrombus (I) | 1 | 0 | 2 | 2 | 1 |
| Amyloid | 1 | 0 | 1 | 2 | 3 |
| Angiectasis | 1 | 0 | 4 | 1 | 2 |
| Mural cyst | 1 | 0 | 0 | 1 | 0 |
| Vasculitis/perivasculitis | 0 | 0 | 1 | 0 | 0 |
| Congestion/hemmorhage | 0 | 0 | 1 | 1 | 0 |
| M-adenocarcinoma | 0 | 1 | 0 | 0 | 0 |

Table C.2.2.15. Histopathological Examination of Female Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| Terminal Sacrifice | | | | | |
| Liver | n=35 | n=39 | n=33 | n=34 | n=28 |
| Not remarkable | 2 | 1 | 0 | 0 | 0 |
| M-hepatocellular carcinoma | 0 | 0 | 0 | 0 | 1 |
| B-hepatocellular adenoma | 1 | 0 | 0 | 0 | 3 |
| M-hemangiosarcoma | 1 | 0 | 0 | 0 | 0 |
| B-hemangioma | 1 | 0 | 0 | 0 | 0 |
| N-hemangiosarcoma | 0 | 0 | 0 | 0 | 1 |
| X-malignant lymphoma | 0 | 0 | 0 | 0 | 0 |
| Focus (I) of cell alteration | 0 | 0 | 0 | 0 | 0 |
| Areas (S) of cell alteration | 0 | 0 | 0 | 0 | 1 |
| Focal hyperplasia | 0 | 0 | 0 | 0 | 1 |
| Diffuse hepatocytic enlargement | 0 | 0 | 0 | 0 | 17 |
| Centrolobular hepatocytic enlargement | 2 | 1 | 0 | 1 | 0 |
| Hepatocytic pigmentation | 2 | 0 | 0 | 6 | 20 |
| Sinusoidal cell pigmentation | 10 | 10 | 10 | 21 | 20 |
| Focal pigmented macrophages | 14 | 21 | 19 | 25 | 24 |
| Amyloid | 4 | 9 | 11 | 12 | 6 |
| Focal mononuclear infiltration | 23 | 25 | 22 | 28 | 22 |
| Focal hepatitis | 29 | 29 | 23 | 24 | 24 |
| Bile duct hyperplasia | 0 | 0 | 0 | 0 | 0 |
| Coagulative necrosis | 1 | 4 | 3 | 1 | 5 |
| Hepatocytic vacuolization | 0 | 4 | 0 | 0 | 3 |
| Extramedullary hematopoiesis | 3 | 4 | 5 | 8 | 5 |
| Chronic infarct | 0 | 0 | 0 | 0 | 0 |
| Centrolobular hepatocytic vacuolation | 1 | 0 | 0 | 0 | 0 |
| Hemorrhage | 1 | 0 | 0 | 0 | 0 |
| Sinusoidal cell hyperplasia | 0 | 0 | 0 | 0 | 0 |
| Mineralization | 0 | 0 | 0 | 0 | 1 |
| Bile duct ectasia | 3 | 0 | 0 | 0 | 0 |
| Fibrosis | 0 | 0 | 0 | 0 | 1 |
| Vascular congestion | 0 | 0 | 0 | 0 | 0 |
| Necrosis of individual hepatocytes | 0 | 1 | 1 | 1 | 0 |
| Individual megacytic hepatocytes | 0 | 0 | 0 | 0 | 0 |
| Focal hypertrophy of hepatocytes | 0 | 0 | 1 | 0 | 0 |

**Nippon Experimental Medical Research Institute, 1983b**. Pregnant rats of strain Jcl:SD aged 10-12 weeks at the beginning of the experiment were administered quizalofop-ethyl by oral gavage on days 6-15 of gestation, at dose levels of 0 (control), 30, 100 or 300 mg/kg/day, as described in Section C.1.2.

The two male and two female pups from each litter were used in a test of reproductive ability at age 10 weeks. Male and female pairs were established within treatment groups, with sibling pairs being avoided. Pairs were co-housed for 10 days for breeding. If the female did not become pregnant, breeding was repeated as follows. For the male, an untreated multiparous female was added to the pair for 10 days; if the male failed to mate or induce pregnancy in one of the females, he was paired with two different females for another 10 days. The female from the original pair was paired for 10 days with a male which had proven reproductive ability from the same treatment group. If no such male was available, the female was paired with an untreated male of proven breeding ability. If pregnancy did not result, the process was repeated for a further 10 days with a different male. The results of the test of reproductive ability are summarized in Table C.1.2.17. There were no significant differences in reproductive ability between the control and any of the treatment groups.

*C.2.3 Other Relevant Data*

The general pharmacokinetics of quizalofop-ethyl in rats are described in section B.4. Quizalofop-ethyl is absorbed to a considerable extent after oral administration. Peak plasma or blood levels occur six to nine hours after administration, with decay around 20 to 30 hours. Quizalofop-ethyl and/or its metabolites are distributed to all tissues tested, including ovary and uterus (see Table B.4.2.2). Concentrations in ovary and uterus were in the middle of the range of tissues tested, indicating no excess accumulation or protection.

***C.2.4 Integrative Evaluation***

Potential effects of quizalofop-ethyl on female reproductive organs were assessed in dog, rat and mouse chronically or subchronically exposed to quizalofop-ethyl in diet. Five studies were reviewed; two in dogs, two in rats and one in mice. The study parameters and outcomes are summarized in Table C.3.4.1. Where parameters were assessed at more than one timepoint, the values at the end of the treatment period are summarized.

Evaluations of gross pathology and histopathology did not reveal any effects on ovaries or uterus in either the first dog study (Nippon Experimental Medical Research Institute, 1982) or the second dog study (Nissan Chemical Industries, Ltd., 1985d). Both studies were of parallel design except for duration of exposure. Ovarian weights varied from control values in both studies, but there was no apparent dose-response relationship and the effects were not reported to be statistically significant. Uterine weights were reported only in the first study (Nippon Experimental Medical Research Institute, 1982). While they varied markedly from control values, there was again no apparent dose-response relationship and the effects were not reported to be statistically significant.

Two studies in Sprague-Dawley rats, one in which the animals were exposed to levels of up to 1280 ppm quizalofop-ethyl in diet for 13 weeks (Nissan Chemical Industries, Ltd., 1982) and another in which the animals were exposed to lower concentrations for a much longer period, up to 400 ppm for 104 weeks, did not show any evidence of effects on female reproductive organs (Nissan Chemical Industries, Ltd., 1985e).

The only study in mice reviewed showed significantly increased ovarian weights at all dose levels. This effect was statistically significant for all dose groups after 78 weeks of exposure to quizalofop-ethyl, and there was also a non-significant increase in ovarian weight in all groups at interim sacrifice following 52 weeks of exposure. There was no clear evidence of other effects on the ovaries or uterus, although there was an increase in the incidence of ovarian hemorrhage after 78 weeks of exposure at the highest dose tested (Nissan Chemical Industries, Ltd., 1985f).

The only available study in which reproductive capability of animals exposed to quizalofop-ethyl was assessed was a study in rats exposed developmentally via administration of quizalofop-ethyl to their dams on days 6-15 of gestation (Nippon Experimental Medical Research Institute, 1983b). Animals were bred at age 10 weeks. No effects on reproductive parameters or pregnancy outcome were observed following maternal exposures of up to 300 mg/kg/day.

Table C.2.4.1. Summary of Reported Effects on Ovaries and Uterus.

| Species | Dose Levels | Duration/ Period of Exposure | Effect on Ovarian and Uterine Weight (% control weight) | Effect on Gross Ovarian/ Uterine Morphology | Effect on Ovarian/ Uterine Histopathology | Study |
|---|---|---|---|---|---|---|
| Dog (Beagle) (n=6) | 0, 25, 100, 400 ppm (diet) [0, 0.82, 3.17, 12.39 mg/kg/ day] | 26 weeks (age 7-13 months) | Ovary<br>25ppm: 90%<br>100: 57%<br>400: 101%<br>Uterus<br>25ppm: 79%<br>100: 31%<br>400: 155% | Not assessed | No treatment-related effects | NEMRI, 1982 |
| Dog (Beagle) (n=6) | 0, 25, 100, 400 ppm (diet) | 52 weeks (age 7-19 months) | Ovary<br>25ppm: 101%<br>100: 100%<br>400: 83% | No apparent effect | No apparent effect | NCI, 1985d |
| Rat (Sprague-Dawley) (n=15) | 0, 40, 128, 1280 ppm (diet) [0, 3.0, 9.7, 93.6 mg/kg/ day] | 13 weeks (age 5-18 weeks) | Ovary<br>40ppm: 87%<br>128: 99%<br>1280: 92%<br>Uterus<br>40ppm: 110%<br>128: 106%<br>1280: 108% | No treatment-related effects | No apparent effect | NCI, 1982 |
| Rat (Sprague-Dawley) (n=50) | 0, 25, 100, 400 ppm (diet) [0, 1.1, 4.6, 18.6 mg/kg/ day] | 105 weeks (age 5-110 weeks) | Ovary<br>25ppm: 95%<br>100: 107%<br>400: 105%<br>Uterus<br>25ppm: 84%[1]<br>100: 89%[1]<br>400: 110%[1] | No apparent effect | No apparent effect | NCI, 1985e |

Table C.2.4.1. Summary of Reported Effects on Ovaries and Uterus (continued).

| Species | Dose Levels | Duration/ Period of Exposure | Effect on Ovarian and Uterine Weight (% control weight) | Effect on Gross Ovarian/ Uterine Morphology | Effect on Ovarian/ Uterine Histopathology | Study |
|---|---|---|---|---|---|---|
| Mouse (CD-1) (n=50) | 0, 2, 10, 80, 320 ppm (diet) [0, N/R[3], 1.88, N/R, 58.47 mg/kg/ day] | 78 weeks (age 6-84 weeks) | Ovary<br>2ppm: 207%*[2]<br>10: 261%*[2]<br>80: 218%*[2]<br>320: 200%*[2] | No apparent effect | Increased incidence of ovarian hemorrhage in 320 ppm animals, not statistically significant or considered to be treatment related | NCI, 1985f |

** statistically significantly different from control value*
*[1] statistically significant decreases reported at 26 and 78 week interim sacrifices, but not at 52 week interim or 105 week terminal sacrifices (terminal values shown).*
*[2] no statistically significant changes reported at 26 and 52 week interim sacrifices (terminal values shown).*
*[3] not included in study report*

## C.3. Male Reproductive Toxicity

### *C.3.1 Human Male Reproductive Toxicology Studies*

No studies or reports pertaining to male reproductive toxic effects of quizalofop-ethyl in humans were identified on the basis of comprehensive computerized literature searches.

### *C.3.2. Animal Male Reproductive Toxicology Studies*

Male reproductive toxicity in dogs identified as atrophy of seminiferous tubules in a 26 week feeding study was the basis for identification of quizalofop-ethyl as causing reproductive toxicity under TRI (Nippon Experimental Medical Research Institute, 1982). In addition to this study, a 52 week feeding study in dogs is available, as are a 90 day feeding studies in rats, an 18 month feeding study in mice and a two year feeding study in rats. None of these other studies were cited under TRI. A multigeneration reproduction study in rats cited under TRI and referenced in the U.S. EPA Integrated Risk Information Service (IRIS) could not be retrieved. Reproductive capability was also investigated in rats exposed to quizalofop-ethyl *in utero*, as discussed in Section C.1.2.

Subchronic and chronic feeding studies: Testicular pathology

**Nippon Experimental Medical Research Institute, 1982**. In this study cited by U.S. EPA under TRI, beagle dogs were administered quizalofop-ethyl in feed for a period of 26 weeks. Both male and female dogs were included in the study, with 6 animals of each sex per treatment group. Animals were randomly distributed among groups, with the exception that siblings were not included in the same treatment group. Concentrations of quizalofop-ethyl in feed were 0 ppm (controls), 25 ppm, 100 ppm and 400 ppm; thus, a total of 24 male and 24 female animals were used. (The concentration of 100 ppm was reported to correspond to 3.20 mg/kg/day for males and 3.17 mg/kg/day for females, while the concentration of 400 ppm was reported to correspond to a 12.75 mg/kg/day for males and 12.39 mg/kg/day for females). Animals were approximately 7 months of age at the beginning of the treatment period. Food and water were available *ad libitum*, up to a maximum of 400 g/day of food per animal. Unconsumed food was measured daily, and water intake was measured over a 20 hour period once per week. Animals were observed twice per day for symptoms of toxicity, and were weighed weekly. Blood, stool and urine samples were collected monthly for analysis.

No animals died during the experimental period, and all animals were autopsied at the end of the experimental period. The study report states that, for histopathological examination, all organs were collected from 12 animals of both sexes, except the male and female genital organs which were harvested from six males or females. No other information is provided on how animals were selected for organ harvesting, or how the six males from which genital organs were harvested were distributed across the four experimental groups. Data for organ weights, including genital organs, are summarized on the basis of all experimental animals. Tissues and organs (including testes) that were used for histopathology were preserved in 10% buffered formalin.

Results of histopathological examination of testis and prostate are summarized in Table C.3.2.1. Atrophy of some part of the testis is reported for two males in the 400 ppm group and no animals in the other groups, on the basis of histopathological examination. As noted above, it cannot be determined from the study report how many males from each group were examined. The effect is further described in the text as atrophy of some seminiferous tubules, and it is noted that this change was not so severe as to cause disturbance in spermatogenesis (although no information is provided on how spermatogenesis was assessed). It is also noted in the report that atrophy of some skeletal muscles, pyelitis, hypertrophy of the adrenal cortex, esophagitis and leptomeningitis were induced independently of each other in the 400 ppm group, but not in the other treatment groups or the control group.

Table C.3.2.1. Results of Histopathological Examination of Testis and Prostate from Dogs Exposed to Quizalofop-Ethyl in Diet for 26 Weeks (Nippon Experimental Research Institute, 1982)

| | | Treatment Group | | | |
|---|---|---|---|---|---|
| Organ | Findings | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Testis | Focal inflammation | 1 | 0 | 0 | 1 |
| | Atrophy in some part | 0 | 0 | 0 | 2 |
| Prostate | Retention cyst | 2 | 1 | 0 | 2 |
| | Chronic inflammation | 0 | 1 | 1 | 2 |
| | Atrophy | 0 | 0 | 0 | 1 |

*The number of animals/group examined was not reported.*

Testicular and prostate weights are summarized in Table C.3.2.2. Although there were some variations in testis and prostate weights across groups, these did not appear to be treatment-related and were not statistically significant (t-test).

Table C.3.2.2. Testis and Prostate Weights from Dogs Exposed to Quizalofop-Ethyl in Diet for 26 Weeks (Nippon Experimental Research Institute, 1982)

| Treatment Group | N | Left Testis (g) Mean $\pm$ S.D. | Right Testis (g) Mean $\pm$ S.D. | Prostate (g) Mean $\pm$ S.D. |
|---|---|---|---|---|
| 0 ppm | 6 | 6.54 $\pm$ 1.40 | 6.70 $\pm$ 1.43 | 9.03 $\pm$ 2.84 |
| 25 ppm | 6 | 7.59 $\pm$ 1.32 | 7.69 $\pm$ 0.89 | 13.11 $\pm$ 6.45 |
| 100 ppm | 6 | 7.17 $\pm$ 0.73 | 7.10 $\pm$ 1.00 | 9.04 $\pm$ 2.66 |
| 400 ppm | 6 | 7.82 $\pm$ 1.04 | 7.36 $\pm$ 0.97 | 9.81 $\pm$ 3.35 |

**Nissan Chemical Industries, Ltd., 1985d.** This second feeding study in beagle dogs was conducted over a 52 week period at the same levels of exposure as in the previous study (Nippon Experimental Research Institute, 1982). Six male and six female dogs per dose level were administered 0 ppm (controls), 25 ppm, 100 ppm or 400 pmm quizalofop-ethyl in diet. The experimental design was essentially the same as the previous study, with the exception that a ground diet was used rather than a pelleted diet. Insufficient information is provided in the two study reports to allow comparison of the dietary composition in the two studies.

One male in the control group died during the course of the study, reportedly for no discernable reason. The death was not considered to be treatment related. All other animals were sacrificed at the end of the experimental period, and all animals were necropsied (although data from animals that died prematurely are not provided). Organs were harvested from all animals in this study, including those that died during the treatment period. Mean gonad weights were reported, and are summarized in Table

C.3.2.3. No statistical analysis appears to have been performed on these data by the study authors.

Tissues and organs (including testes) that were used for histopathology were preserved in 10% neutral buffered formalin. The results of histological examinations were reported only when pathological findings occurred. Pathology of male reproductive organs reported is summarized in Table C.3.2.4. There appeared to be no treatment-related effects.

Table C.3.2.3. Gonad Weights from Dogs Exposed to Quizalofop-Ethyl in Diet for 52 Weeks (Nissan Chemical Industries, Ltd., 1985d)

| Treatment Group | N | Left Gonads (g) Mean ± S.D. (organ/body weight ratio, %) | Right Gonads (g) Mean ± S.D. (organ/body weight ratio, %) | Total (g) Mean ± S.D. (organ/body weight ratio, %) |
|---|---|---|---|---|
| 0 ppm | 6 | 11.5 ± 1.1060 (0.095 ± 0.005) | 11.6 ± 1.232 (0.096 ± 0.004) | 23.1 ± 2.295 (0.191 ± 0.008) |
| 25 ppm | 6 | 9.96 ± 2. 912 (0.078 ± 0.019) | 10.4 ± 1.853 (0.081 ± 0.016) | 20.3 ± 4.110 (0.159 ± 0.034) |
| 100 ppm | 6 | 10.3 ± 1.246 (0.087 ± 0.014) | 10.2 ± 1.175 (0.086 ± 0.016) | 20.6 ± 2.324 (0.173 ± 0.029) |
| 400 ppm | 6 | 9.88 ± 1.538 (0.081 ± 0.012) | 10.1 ± 1.179 (0.082 ± 0.010) | 19.9 ± 2.650 (0.163 ± 0.022) |

Table C.3.2.4. Results of Histopathological Examination of Male Reproductive Organs from Dogs Exposed to Quizalofop-Ethyl in Diet for 52 Weeks (Nissan Chemical Industries, Ltd., 1985d)

| | | Treatment Group | | | |
|---|---|---|---|---|---|
| Organ | Findings | 0 ppm (control) (n=5) | 25 ppm (n=6) | 100 ppm (n=6) | 400 ppm (n=6) |
| Epididymis | Mineralization | 0 | 1 | 0 | 0 |
| | Sperm granuloma | 0 | 0 | 0 | 1 |
| | Epididymitis | 1 | 0 | 0 | 0 |
| Prostate | Cyst | 1 | 0 | 0 | 0 |
| | Prostatitis | 1 | 0 | 1 | 1 |

*No data on testes were included in the report, indicating that no histopathological effects were observed in any animals of any groups.*

Food and water consumption in this study were reported to have been unaffected by treatment, and there were no treatment-related changes in clinical condition or behavior.

The authors of the study report considered the highest dose tested, 400 ppm, to be a no effect level.

**Nissan Chemical Industries, Ltd., 1982.** Male and female Sprague-Dawley rats were administered 0 (control), 40, 128 or 1280 ppm quizalofop-ethyl in diet for a period of 13 weeks, beginning when the animals were approximately five weeks of age. These dietary concentrations corresponded to average intakes of 0, 2.6, 8.4 and 82.9 mg/kg/day by males over the 13 week exposure period. Animals were randomly distributed among treatment groups, with 20 males and 20 females/group. Fifteen animals of each sex/group were scheduled for sacrifice at the end of the exposure period, while the remaining five animals were allowed a six week recovery period before sacrifice.

Animals had free access to tap water and diet. Clinical observations were made daily for each animal during the first four weeks of treatment, then weekly thereafter. Food intake was measured weekly on the basis of total intake/cage (5 animals/cage), and water intake was measured on a daily basis during weeks five and 10 of treatment. Individual animals were weighed weekly. Urine samples were collected from 10 males/group during weeks three and 11 of treatment, and blood samples were taken from 10 lightly-anesthetized males per group on weeks four and 12 of treatment.

No male animals died during the course of treatment or the recovery period. No clinical findings were noted during the course of the study that were considered to be treatment-related, and the behavior and appearance of the treated animals was reported to be the same as that of the controls.

Testes weights were significantly reduced in males treated with 1280 ppm quizalofop-ethyl, compared to controls (Table C.3.2.5), both in animals sacrificed at the end of the treatment period and in animals sacrificed after a 6 week recovery period. No effect on testes weights was observed in other treatment groups. Macroscopic examination of the testes identified 12/15 males in the 1280 ppm group as having small testes, and 4/15 as having flaccid testes at the end of the treatment period; additionally, 4/5 males in the 1280 ppm group were identified as having small and/or flaccid testes at the end of the 6 week recovery period, as was 1/5 males in the 128 ppm group. No such treatment-related observations were reported for any other animals in the control or other treatment groups. A single incidence of unilateral testicular atrophy in a control animal, which was considered to be possibly traumatic in origin, was reported, while an animal in the 40 ppm group had unilateral, complete testicular atrophy possibly due to an undescended testis. Tissues and organs (including testes) that were used for histopathology were preserved in 10% buffered formalin. Microscopic histopathological examination of the testes identified testicular atrophy and/or suppression of spermatogenesis in 13/15 males in the 1280 ppm group at the end of the treatment period, with no such effects observed in any of the other groups. Three of five animals in the 1280 ppm group also showed testicular atrophy and/or suppression of spermatogenesis at the end of the six week recovery period.

Table C.3.2.5. Testes Weights from Rats Exposed to Quizalofop-Ethyl in Diet for 13 Weeks (Nissan Chemical Industries, Ltd., 1982)

| Treatment Group | Testes Weight (g) at End of 13 Week Treatment (n=15) Mean ± S.D. | Testes Weight (g) After 6 Week Recovery (n=5) Mean ± S.D. |
|---|---|---|
| 0 ppm | 4.4 ± 0.32 | 4.5 ± 0.30 |
| 40 ppm | 4.6 ± 0.63 | 4.6 ± 0.26 |
| 128 ppm | 4.5 ± 0.36 | 4.6 ± 0.51 |
| 1280 ppm | 2.7 ± 0.70** | 2.8 ± 0.87** |

*** p<0.001 by Student's t-test; p<0.01 by William's test*

In addition to effects on the testes, males in the 1280 ppm group differed from controls in a number of parameters. Food intake and body weight gain during the treatment period were significantly reduced in the 1280 ppm males ($p<0.001$ for both parameters), as summarized in Table C.3.2.6. Food utilization was also marginally reduced in this group. Reduced food intake was observed from the beginning of the exposure period, and it was suggested that this was primarily due to unpalatability of the compound. There was also some indication of reduced food utilization (i.e., reduced weight gain/unit food ingested) in the 1280 ppm treatment group. Water intake was not significantly affected in this treatment group.

Males in the 1280 ppm group showed no traces of protein in urine compared to normal protein levels in urine from the other groups. During weeks four and 12, males in the 1280 ppm group had significantly lower red blood cell counts compared to controls ($p<0.01$), with hemoglobin concentration also reduced during week four ($p<0.01$). Finally, liver weight (Table C.3.2.7) and condition (Table C.3.2.8) were affected in both the 128 and 1280 ppm animals sacrificed at the end of the treatment period, with the severity of the effect increasing with dose. Animals sacrificed after the six week recovery period were reported to have completely recovered from these effects. As noted above, only the incidence of abnormal findings was reported.

Table C.3.2.6. Body Weight Gain and Food and Water Intake in Male Rats Exposed to Quizalofop-Ethyl in Diet for 13 Weeks (Nissan Chemical Industries, Ltd., 1982)

| Treatment Group | | 0 ppm (control) | 40 ppm | 128 ppm | 1280 ppm |
|---|---|---|---|---|---|
| | | | | | |
| Bodyweight Gain over the 13 Week Treatment Period (g) Mean ± S.D. (n) | | 361 ± 53.6 (15) | 370 ± 47.1 (15) | 379 ± 41.2 (15) | 266 ± 41.1 (15) |
| Food Intake (g/rat) over the 13 Week Treatment Period Mean ± S.D. (n) | | 2056 ± 79.5 (15) | 2057 ± 117.8 (15) | 2110 ± 82.1 (15) | 1751 ± 39.3 *** (15) |
| Water Consumption (ml/rat/week) on Week 5 of Treatment Mean ± S.D. (n) | | 242.8 ± 14.37 (15) | N/R[1] | N/R | 258.4 ± 29.02 (15) |
| Water Consumption (ml/rat/week) on Week 10 of Treatment Mean ± S.D. (n) | | 237.8 ± 13.77 (15) | N/R | N/R | 216.3 ± 20.57 (15) |
| | | | | | |
| Bodyweight Gain over the 6 Week Recovery Period (g) Mean ± S.D. (n) | | 57 ± 16.6 (5) | 48 ± 16.5 (5) | 55 ± 19.7 (5) | 119 ± 43.0 (5) |
| Food Intake (g/rat) over the 6 Week Recovery Period Mean (n) | | 1012 (5) | 959 (5) | 996 (5) | 1053 (5) |

*** *p<0.001, Student's t-test*

[1] *Not reported*

Table C.3.2.7. Liver Weights in Male Rats Exposed to Quizalofop-Ethyl in Diet for 13 Weeks (Nissan Chemical Industries, Ltd., 1982)

| Treatment Group | Liver Weight (g) at End of 13 Week Treatment (n=15) Mean ± S.D. | Liver Weight (g) After 6 Week Recovery (n=5) Mean ± S.D. |
|---|---|---|
| 0 ppm | 20.91 ± 3.450 | 22.30 ± 2.280 |
| 40 ppm | 21.41 ± 3.069 | 19.64 ± 4.328* |
| 128 ppm | 23.26 ± 2.677 | 22.34 ± 1.781 |
| 1280 ppm | 30.61 ± 3.971** | 22.16 ± 2.943 |

* *p<0.05 by Student's t-test (not confirmed by William's test), compared to control level*

** *p<0.001 by Student's t-test; p<0.01 by William's test, compared to control level*

Table C.3.2.8. Liver Condition in Male Rats Exposed to Quizalofop-Ethyl in Diet for 13 Weeks (Nissan Chemical Industries, Ltd., 1982)

| | | Treatment Group (End of 13 Week Treatment Period) | | | |
|---|---|---|---|---|---|
| Organ | Findings | 0 ppm (control) (n=15) | 40 ppm (n=15) | 128 ppm (n=15) | 1280 ppm (n=15) |
| Liver | Enlarged | 0 | 0 | 1 | 15 |
| | Surface pitted | 0 | 0 | 2 | 13 |
| | Brown discolored | 0 | 0 | 0 | 2 |
| | Swollen | 0 | 1 | 1 | 0 |
| | Pale | 1 | 0 | 0 | 0 |
| | | Treatment Group (End of 6 Week Recovery Period) | | | |
| | | 0 ppm (control) (n=5) | 40 ppm (n=5) | 128 ppm (n=5) | 1280 ppm (n=15) |
| Liver | Surface pitted | 0 | 0 | 0 | 1 |

**Nissan Chemical Industries, Ltd., 1985e.** Male and female Sprague-Dawley rats were administered 0 (control), 25, 100 or 400 ppm quizalofop-ethyl in diet for a period of 104 weeks for males and 105 weeks for females, beginning when the animals were approximately five weeks of age. These dietary concentrations corresponded to average intakes of 0, 0.9, 3.7 and 15.5 mg/kg/day by males over the treatment period. Animals were randomly distributed among treatment groups, with 50 males and 50 females/group. Satellite groups of 35 animals of each sex were maintained at each exposure level, and were sacrificed at interim timepoints. Ten males and 10 females were sacrificed after 26 weeks of treatment, and 10 more animals of each sex after 52 weeks of treatment. The remaining satellite animals were killed after 78 weeks of treatment.

Animals had free access to tap water and diet. Clinical observations were made daily for each animal during the first four weeks of treatment, then weekly thereafter. Food intake was measured weekly on the basis of total intake/cage (5 animals/cage), and water intake was measured on a daily basis during weeks 11 and 24 of treatment. Individual animals were weighed weekly.

There were no clinical observations made during the treatment period that were considered to reflect treatment-related changes. Food and water intakes did not differ significantly between control and any treatment groups. Mortality across the treatment period is summarized in Table C.3.2.9. There were no significant differences in mortality between control and any treatment groups.

Table C.3.2.9. Mortality in Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| Number of Deaths during Weeks (%) | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 1-26 | 0/50 (0) | 0/50 (0) | 0/50 (0) | 1/50 (2) |
| 27-52 | 1/50 (2) | 2/50 (4) | 0/50 (0) | 1/49 (2) |
| 53-78 | 7/49 (14) | 10/48 (21) | 13/50 (26) | 17/48 (35) |
| 79-106 | 25/42 (60) | 17/38 (45) | 17/37 (46) | 14/31 (45) |
| 1-106 | 33/50 (66) | 29/50 (58) | 30/50 (60) | 33/50 (66) |

Weight gain over the periods from 0-78 and 0-105 weeks of treatment is summarized in Table C.2.3.10. The slight decrease in weight gain recorded for males in the 400 ppm group over the first 78 weeks of treatment did not attain statistical significance, nor did the greater weight gain in these animals over the entire 105 week treatment period.

Table C.3.2.10. Weight Gain in Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| Mean Weight Gain (g) Between Weeks | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 0-78 | 670 | 664 | 663 | 649 |
| 0-105 | 552 | 594 | 663 | 728 |

The results of macroscopic examination of reproductive organs are summarized in Table C.3.2.11, organ weights (reproductive organs and any other organs where significant effects were observed) are summarized in Table C.3.2.12 and results of histopathology of the reproductive organs are summarized in Table C.3.2.13. Tissues and organs (including testes) that were used for histopathology were preserved in 10% buffered formalin. There were no apparent treatment-related effects on male reproductive organs at any of the timepoints examined in this study. Liver weight was significantly increased in male rats receiving 400 ppm quizalofop-ethyl at 52 and 78 weeks; the increase in liver weight at 105 weeks was not statistically significant.

Table C.3.2.11. Macroscopic Pathology Examination of Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Found dead or sacrificed *in extremis* | n=2 | n=1 | n=3 | n=4 |
| Prostate | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Testis/es | | | | |
| Mass/es | 0 | 0 | 0 | 0 |
| Excrescences | 0 | 0 | 0 | 0 |
| Small | 0 | 0 | 1 | 0 |
| Flaccid | 0 | 0 | 1 | 0 |
| 26 Week Interim Sacrifice | n=10 | n=10 | n=10 | n=10 |
| Prostate | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Testis/es | | | | |
| Mass/es | 0 | 0 | 0 | 0 |
| Excrescences | 0 | 0 | 0 | 0 |
| Small | 0 | 0 | 0 | 1 |
| Flaccid | 0 | 0 | 0 | 1 |
| 52 Week Interim Sacrifice | n=10 | n=10 | n=10 | n=10 |
| Prostate | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Testis/es | | | | |
| Mass/es | 0 | 0 | 0 | 0 |
| Excrescences | 0 | 0 | 0 | 0 |
| Small | 0 | 0 | 0 | 0 |
| Flaccid | 0 | 0 | 0 | 0 |

Table C.3.2.11. Macroscopic Pathology Examination of Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued).

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 78Week Interim Sacrifice | n=13 | n=14 | n=12 | n=11 |
| Prostate | | | | |
| Mass | 0 | 0 | 0 | 0 |
| Testis/es | | | | |
| Mass/es | 1 | 0 | 0 | 1 |
| Excrescences | 0 | 0 | 0 | 0 |
| Small | 1 | 3 | 1 | 0 |
| Flaccid | 1 | 3 | 1 | 1 |
| Terminal Sacrifice | | | | |
| Prostate | n=17 | n=21 | n=20 | n=17 |
| Mass | 0 | 0 | 0 | 0 |
| Testis/es | | | | |
| Mass/es | 0 | 0 | 4 | 1 |
| Excrescences | 2 | 0 | 0 | 0 |
| Small | 1 | 7 | 2 | 2 |
| Flaccid | 2 | 6 | 2 | 3 |
| Found dead or sacrificed *in extremis* (between weeks 78 and 105) | n=33 | n=29 | n=30 | n=33 |
| Prostate | | | | |
| Mass | 1 | 0 | 0 | 0 |
| Testis/es | | | | |
| Mass/es | 2 | 0 | 0 | 1 |
| Excrescences | 0 | 0 | 0 | 0 |
| Small | 5 | 7 | 6 | 0 |
| Flaccid | 2 | 3 | 3 | 0 |

Table C.3.2.12. Organ Weights from Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 26 Week Interim Sacrifice | | | | |
| Mean Testes Weight (g) | 5.15 | 4.92 | 5.18 | 5.27 |
| Mean Liver Weight (g) | 23.6 (23.8)[1] | 24.0 (23.5) | 24.2 (24.3) | 33.1**(33.3) |
| Mean Kidneys Weight (g) | 4.37 (4.39) | 4.52 (4.47) | 4.40 (4.41) | 4.88**(4.90) |
| Mean Thyroids Weight (mg) | 28 | 28 | 30 | 22* |
| Mean Thymus Weight (g) | 0.24 | 0.18 | 0.24 | 0.18 |
| Mean Spleen Weight (mg) | 0.90 (0.90) | 0.85 (0.84) | 0.90 (0.90) | 0.79 (0.79) |
| 52 Week Interim Sacrifice | | | | |
| Mean Testes Weight (g) | 5.08 | 5.09 | 5.29 | 5.23 |
| Mean Liver Weight (g) | 28.6 (28.3) | 28.4 (28.4) | 31.7 (33.2) | 35.8**(34.7) |
| Mean Kidneys Weight (g) | 5.30 (5.27) | 5.18 (5.18) | 5.46 (5.62) | 5.58 (5.46) |
| Mean Thyroids Weight (mg) | 38 (38) | 33 (33) | 40 (41) | 37 (36) |
| Mean Thymus Weight (g) | 0.12 | 0.09 | 0.08* | 0.08* |
| Mean Spleen Weight (mg) | 1.04 (1.03) | 1.05 (1.05) | 0.94 (0.97) | 0.96 (0.94) |
| 78Week Interim Sacrifice | | | | |
| Mean Testes Weight (g) | 5.15 (5.12) | 4.53 (4.63) | 5.52 (5.45) | 5.73 (5.72) |
| Mean Liver Weight (g) | 30.7 (30.3) | 29.6 (30.8) | 28.0 (27.2) | 35.0*(34.9) |
| Mean Kidneys Weight (g) | 6.10 | 6.51 | 5.44 | 6.03 |
| Mean Thyroids Weight (mg) | 42 (42) | 48 (49) | 45 (44) | 43 (43) |
| Mean Thymus Weight (g) | 0.09 | 0.08 | 0.10 | 0.08 |
| Mean Spleen Weight (mg) | 1.40 (1.40) | 1.13 (1.19) | 1.28 (1.25) | 1.05**(1.05) |
| Terminal Sacrifice (Week 104/105) | | | | |
| Mean Testes Weight (g) | 5.16 (5.16) | 4.50 (4.46) | 5.34 (5.30) | 4.82 (4.92) |
| Mean Liver Weight (g) | 26.7 (27.4) | 24.9 (25.0) | 28.7 (29.6) | 29.4 (31.2) |
| Mean Kidneys Weight (g) | 6.48 (6.50) | 5.97 (5.93) | 6.79 (6.75) | 6.05 (6.13) |
| Mean Thyroids Weight (mg) | 41 (43) | 47 (47) | 48 (49) | 56**(63) |
| Mean Thymus Weight (g) | 0.10 | 0.10 | 0.09 | 0.10 |
| Mean Spleen Weight (mg) | 1.38 (1.38) | 1.19 (1.17) | 1.22 (1.21) | 1.09**(1.13) |

** $p<0.05$ ** $p<0.01$ (Williams' test), compared to control value*

[1] *Where organ weights were adjusted for bodyweight as a covariate during statistical analysis, the unadjusted mean is shown in parentheses.*

Table C.3.2.13. Histopathology Examination of Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e)

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 26 Week Interim Sacrifice | | | | |
| Seminal Vesicles | n=10 | n=9 | n=10 | n=10 |
| Not remarkable | 10 | 9 | 10 | 9 |
| Epithelial hyperplasia | 0 | 0 | 0 | 1 |
| Vesiculitis | 0 | 0 | 0 | 0 |
| Testes | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 10 | 10 | 10 | 10 |
| Testicular atrophy | 0 | 0 | 0 | 1 |
| Cell debris in tubules | 0 | 0 | 0 | 1 |
| Arterial medial calcification | 0 | 0 | 0 | 0 |
| Tubular mineralization | 0 | 0 | 0 | 0 |
| Atrophic tubules | 0 | 0 | 0 | 0 |
| Dilated tubules | 0 | 0 | 0 | 0 |
| Arrest of spermatogenesis | 0 | 0 | 0 | 0 |
| Interstitial cell hyperplasia | 0 | 0 | 0 | 0 |
| Medial degeneration/periarteritis | 0 | 0 | 0 | 0 |
| Atrophy | 0 | 0 | 0 | 0 |
| Ectopic adipose tissue | 0 | 0 | 0 | 0 |
| Giant spermatids in tubules | 0 | 0 | 0 | 0 |
| 52 Week Interim Sacrifice | | | | |
| Seminal Vesicles | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 10 | 10 | 9 | 10 |
| Epithelial hyperplasia | 0 | 0 | 0 | 0 |
| Vesiculitis | 0 | 0 | 1 | 0 |
| Testes | n=10 | n=10 | n=10 | n=10 |
| Not remarkable | 8 | 8 | 8 | 9 |
| Testicular atrophy | 0 | 0 | 0 | 0 |
| Cell debris in tubules | 0 | 0 | 0 | 0 |
| Arterial medial calcification | 2 | 0 | 0 | 0 |
| Tubular mineralization | 0 | 2 | 0 | 1 |
| Atrophic tubules | 0 | 0 | 1 | 1 |
| Dilated tubules | 0 | 0 | 1 | 0 |
| Arrest of spermatogenesis | 0 | 0 | 1 | 0 |
| Interstitial cell hyperplasia | 0 | 0 | 0 | 0 |
| Medial degeneration/periarteritis | 0 | 0 | 0 | 0 |
| Atrophy | 0 | 0 | 0 | 0 |
| Ectopic adipose tissue | 0 | 0 | 0 | 0 |
| Giant spermatids in tubules | 0 | 0 | 0 | 0 |

Table C.3.2.13. Histopathology Examination of Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued).

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| 78Week Interim Sacrifice | | | | |
| Seminal Vesicles | n=13 | n=14 | n=12 | n=11 |
| Not remarkable | 13 | 14 | 12 | 11 |
| Epithelial hyperplasia | 0 | 0 | 0 | 0 |
| Vesiculitis | 0 | 0 | 0 | 0 |
| Testes | n=13 | n=14 | n=12 | n=11 |
| Not remarkable | 7 | 7 | 10 | 6 |
| Testicular atrophy | 0 | 0 | 0 | 0 |
| Cell debris in tubules | 0 | 0 | 0 | 0 |
| Arterial medial calcification | 2 | 1 | 0 | 0 |
| Tubular mineralization | 0 | 2 | 1 | 1 |
| Atrophic tubules | 2 | 0 | 1 | 0 |
| Dilated tubules | 0 | 0 | 0 | 1 |
| Arrest of spermatogenesis | 0 | 0 | 0 | 0 |
| Interstitial cell hyperplasia | 2 | 2 | 0 | 2 |
| Medial degeneration/periarteritis | 1 | 1 | 0 | 1 |
| Atrophy | 0 | 3 | 1 | 1 |
| Ectopic adipose tissue | 0 | 1 | 0 | 0 |
| Giant spermatids in tubules | 0 | 0 | 1 | 0 |

Table C.3.2.13. Histopathology Examination of Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued).

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Terminal Sacrifice (105 Weeks) | | | | |
| Seminal Vesicles | n=17 | n=21 | n=20 | n=17 |
| Not remarkable | 16 | 20 | 17 | 17 |
| Autolysis | 0 | 0 | 0 | 0 |
| Epithelial hyperplasia | 0 | 0 | 0 | 0 |
| Vesiculitis | 0 | 0 | 0 | 0 |
| Collapsed | 0 | 0 | 0 | 0 |
| Medial degeneration/periarteritis | 0 | 0 | 0 | 0 |
| Distended | 0 | 0 | 0 | 0 |
| Interstitial inflammation | 0 | 0 | 0 | 0 |
| Atrophy | 0 | 0 | 1 | 0 |
| Reduction in secretion | 0 | 1 | 2 | 0 |
| Testes | n=17 | n=21 | n=20 | n=17 |
| Not remarkable | 6 | 6 | 2 | 5 |
| Autolysis | 0 | 0 | 0 | 0 |
| Testicular atrophy | 0 | 0 | 0 | 0 |
| Arterial medial calcification | 4 | 6 | 5 | 9 |
| Tubular mineralization | 0 | 0 | 0 | 0 |
| Atrophic tubules | 3 | 3 | 3 | 1 |
| Interstitial cell hyperplasia | 2 | 3 | 1 | 3 |
| Medial degeneration/periarteritis | 3 | 4 | 6 | 2 |
| Atrophy | 1 | 5 | 2 | 2 |
| Calcification in tubules | 1 | 4 | 4 | 0 |
| Arrest of spermatogenesis | 0 | 0 | 0 | 1 |
| Spermatocele | 0 | 0 | 0 | 0 |
| Giant spermatids in tubules | 1 | 0 | 0 | 1 |
| Infarction | 0 | 0 | 0 | 0 |
| Mesothelial proliferation | 1 | 0 | 0 | 0 |
| Interstitial inflammation/fibrosis | 1 | 0 | 0 | 0 |

Table C.3.2.13. Histopathology Examination of Male Rats Exposed to Quizalofop-Ethyl in Diet for 104 Weeks (Nissan Chemical Industries, Ltd., 1985e) (continued).

| | Treatment Group | | | |
|---|---|---|---|---|
| | 0 ppm (control) | 25 ppm | 100 ppm | 400 ppm |
| Found dead or sacrificed *in extremis* | | | | |
| Seminal Vesicles | n=32 | n=29 | n=30 | n=33 |
| Not remarkable | 26 | 26 | 22 | 32 |
| Autolysis | 3 | 1 | 3 | 0 |
| Epithelial hyperplasia | 0 | 0 | 0 | 0 |
| Vesiculitis | 2 | 0 | 4 | 1 |
| Collapsed | 0 | 1 | 0 | 0 |
| Medial degeneration/periarteritis | 1 | 0 | 0 | 0 |
| Distended | 0 | 1 | 0 | 0 |
| Interstitial inflammation | 1 | 0 | 0 | 0 |
| Atrophy | 0 | 0 | 0 | 0 |
| Reduction in secretion | (illegible) | 0 | 0 | 0 |
| Testes | n=(illegible) | n=29 | n=30 | n=33 |
| Not remarkable | 17 | 15 | 14 | 17 |
| Autolysis | 1 | 1 | 1 | 0 |
| Testicular atrophy | 0 | 0 | 1 | 0 |
| Arterial medial calcification | 2 | 4 | 3 | 8 |
| Tubular mineralization | 2 | 2 | 0 | 0 |
| Atrophic tubules | 6 | 2 | 0 | 3 |
| Interstitial cell hyperplasia | 2 | 1 | 0 | 6 |
| Medial degeneration/periarteritis | 12 | 5 | 5 | 0 |
| Atrophy | 3 | 2 | 5 | 0 |
| Calcification in tubules | 0 | 1 | 1 | 0 |
| Arrest of spermatogenesis | 0 | 1 | 2 | 0 |
| Spermatocele | 0 | 1 | 0 | 0 |
| Giant spermatids in tubules | 0 | 0 | 0 | 0 |
| Infarction | 0 | 1 | 0 | 0 |
| Mesothelial proliferation | 0 | 0 | 0 | 0 |
| Interstitial inflammation/fibrosis | 0 | 0 | 0 | 0 |

**Nissan Chemical Industries, Ltd., 1985f**. Male and female CD-1 mice were administered 0 (control), 2, 10, 80 or 320 ppm quizalofop-ethyl in diet for a period of 78 weeks, beginning when the animals were approximately six and a half weeks of age. (The 10 and 320 ppm concentrations were reported to correspond to 1.55 and 49.77 mg/kg/day, respectively, for male mice; intake levels corresponding to other dietary concentrations were not reported). Animals were randomly distributed among treatment groups, with 50 males and 50 females per group. Two satellite groups (A and B) of 10 animals of each sex per group were maintained at each exposure level, and all surviving animals in these groups were sacrificed at interim timepoints. The surviving animals in satellite group A were sacrificed after 26 weeks of treatment and the surviving animals of satellite group B after 52 weeks of treatment. The animals of the main treatment groups were killed after 78 weeks of treatment.

Clinical observations were made weekly during weeks 1-14 of treatment, and biweekly thereafter. Food consumption was recorded weekly during weeks 1-14 of treatment, and biweekly thereafter. Water intake does not appear to have been measured in this study. Individual animals were weighed weekly during weeks 1-14 of treatment, and biweekly thereafter.

Mortality during the course of treatment in male mice is summarized in Table C.3.2.14. Sacrifice of moribund animals is included, but accidental deaths that were not treatment related are not, nor are scheduled sacrifices. It was reported that there was a significant trend towards reduced survival in treated males, and that the survival rate in males receiving 320 ppm quizalofop-ethyl was significantly lower than the control rate (probability value not given).

Table C.3.2.14. Mortality in Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| Number of Deaths during Weeks (%) | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 0-9 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 1/70 (1.4) | 0 | 0 | 0 |
| 11-13 | 0 | 0 | 0 | 0 | 0 |
| 14 | 0 | 0 | 0 | 0 | 1/70 (1.4) |
| 15-18 | 0 | 0 | 0 | 0 | 0 |
| 19 | 0 | 0 | 0 | 1/69 (1.5) | 1/70 (1.4) |
| 20 | 0 | 0 | 0 | 0 | 0 |
| 21 | 0 | 0 | 0 | 1/69 (1.5) | 0 |
| 22 | 0 | 0 | 0 | 0 | 1/70 (1.4) |
| 23-26 | 0 | 0 | 0 | 0 | 0 |
| 27 | 0 | 1/70 (1.4) | 0 | 0 | 0 |
| 28 | 0 | 0 | 0 | 0 | 1/60 (1.7) |
| 29 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0 | 1/60 (1.7) | 0 | 0 | 0 |
| 31 | 0 | 0 | 0 | 0 | 0 |
| 32 | 0 | 0 | 1/60 (1.7) | 0 | 0 |
| 33 | 0 | 0 | 0 | 0 | 1/60 (1.7) |
| 34 | 1/60 (1.7) | 0 | 0 | 0 | 1/60 (1.7) |
| 35 | 0 | 0 | 0 | 0 | 0 |
| 36 | 0 | 0 | 0 | 0 | 1/60 (1.7) |
| 37-40 | 0 | 0 | 0 | 0 | 0 |
| 41 | 1/60 (1.7) | 0 | 2/60 (3.3) | 0 | 0 |

Table C.3.2.14. Mortality in Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| Number of Deaths during Weeks (%) | Treatment Group | | | | |
|---|---|---|---|---|---|
| 42 | 1/60 (1.7) | 0 | 0 | 0 | 0 |
| 43-44 | 0 | 0 | 0 | 0 | 0 |
| 45 | 1/60 (1.7) | 0 | 0 | 0 | 0 |
| 46 | 0 | 0 | 0 | 1/60 (1.7) | 0 |
| 47 | 0 | 0 | 0 | 0 | 0 |
| 48 | 0 | 0 | 0 | 0 | 1/60 (1.7) |
| 49 | 0 | 0 | 0 | 1/60 (1.7) | 2/60 (3.3) |
| 50-51 | 0 | 0 | 0 | 0 | 0 |
| 52 | 0 | 0 | 0 | 1/60 (1.7) | 0 |
| 53-54 | 0 | 0 | 0 | 0 | 0 |
| 55 | 0 | 1/50 (2.0) | 0 | 1/52 (1.9) | 1/51 (2.0) |
| 56 | 0 | 0 | 0 | 1/52 (1.9) | 0 |
| 57-59 | 0 | 0 | 0 | 0 | 0 |
| 60 | 0 | 0 | 2/51 (3.9) | 1/52 (1.9) | 0 |
| 61 | 0 | 0 | 1/51 (2.0) | 0 | 1/51 (2.0) |
| 62 | 0 | 1/50 (2.0) | 0 | 1/52 (1.9) | 0 |
| 63 | 0 | 2/50 (4.0) | 0 | 0 | 0 |
| 64 | 0 | 0 | 1/51 (2.0) | 1/52 (1.9) | 0 |
| 65 | 0 | 1/50 (2.0) | 0 | 0 | 2/51 (3.9) |
| 66 | 0 | 0 | 0 | 0 | 0 |
| 67 | 0 | 0 | 2/51 (3.9) | 0 | 1/51 (2.0) |
| 68 | 1/50 (2.0) | 0 | 0 | 0 | 0 |
| 69 | 0 | 0 | 0 | 0 | 0 |
| 70 | 1/50 (2.0) | 0 | 0 | 0 | 0 |
| 71 | 1/50 (2.0) | 0 | 0 | 5/52 (9.6) | 0 |
| 72 | 0 | 1/50 (2.0) | 0 | 0 | 1/51 (2.0) |
| 73 | 1/50 (2.0) | 0 | 0 | 0 | 1/51 (2.0) |
| 74 | 1/50 (2.0) | 0 | 1/51 (2.0) | 0 | 0 |
| 75 | 0 | 1/50 (2.0) | 0 | 1/52 (1.9) | 0 |
| 76 | 0 | 0 | 1/51 (2.0) | 0 | 1/51 (2.0) |
| 77 | 0 | 1/50 (2.0) | 0 | 1/52 (1.9) | 3/51 (5.9) |
| 78 | 0 | 0 | 0 | 1/52 (1.9) | 2/51 (3.9) |
| 79 | 0 | 1/50 (2.0) | 0 | 1/52 (1.9) | 0 |
| 80 | 0 | 0 | 0 | 0 | 0 |
| Total deaths/group | 9 | 12 | 11 | 19 | 23 |

There were no apparent treatment-related effects on incidence of clinical signs, other than an possible increase in the incidence of swollen abdomens (14, 22, 17, 16 and 33 cases in the 0, 2, 10, 80 and 320 ppm group males, respectively).

It was reported that body weights across groups were homogeneous at the time of random assignment of animals to groups; however, when treatment began four days after assignment of animals to groups, body weights in the 320 ppm group were significantly below control values and may have influenced subsequent growth analysis. There was no apparent treatment-related effect on body weights or weight gain between treatment groups and controls. The high-dose groups was slightly but significantly heavier than the control groups at several timepoints but, as noted above, this may have been attributable to the slightly lower bodyweight of these animals at the beginning of treatment. Food consumption was also not consistently affected by treatment with quizalofop-ethyl. The only statistically significant differences were greater food intake by the 320 ppm group than controls in weeks 32 and 40 of treatment.

The results of gross pathological examinations of tissues are summarized in Table C.3.2.15, absolute organ weights are summarized in Table C.3.2.16 and relative organ weights are summarized in Table C.3.2.17 (for reproductive organs and other organs where a significant effect was reported). Results of histopathological examinations are summarized in Table C.3.2.18. Tissues and organs (including testes and epididymides) that were used for histopathology were preserved in 10% neutral buffered formalin.

The only gross pathological effect considered to be treatment-related in male mice was the increase in dark and enlarged livers seen in the 320 ppm animals at all timepoints. Any other findings were not considered to be compound-related.

Table C.3.2.15. Gross Pathological Examination of Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | | | | | |
| Testes | n=10 | n=10 | n=9 | n=9 | n=10 |
| Not remarkable | 10 | 10 | 9 | 9 | 10 |
| Epididymides | n=10 | n=10 | n=9 | n=9 | n=10 |
| Not remarkable | 10 | 10 | 9 | 9 | 10 |
| Liver | n=10 | n=10 | n=9 | n=9 | n=10 |
| Not remarkable | 10 | 9 | 8 | 9 | 5 |
| Dark | 0 | 0 | 0 | 0 | 5 |
| Enlarged | 0 | 0 | 0 | 0 | 2 |
| Friable | 0 | 0 | 0 | 0 | 1 |
| Pale | 0 | 0 | 0 | 0 | 0 |
| Pale focus (I)/area(s) | 0 | 0 | 1 | 0 | 0 |
| Dark focus (I)/area(s) | 0 | 1 | 0 | 0 | 0 |
| H- Dark focus (I)/area(s) | 0 | 0 | 0 | 0 | 0 |
| 52 Week Interim Sacrifice | | | | | |
| Testes | n=10 | n=10 | n=9 | n=8 | n=9 |
| Not remarkable | 10 | 10 | 9 | 9 | 8 |
| Dark | 0 | 0 | 0 | 0 | 1 |
| Unequal size | 0 | 0 | 0 | 0 | 1 |
| Flaccid | 0 | 0 | 0 | 0 | 1 |
| Epididymides | n=10 | n=10 | n=9 | n=8 | n=9 |
| Not remarkable | 10 | 10 | 9 | 8 | 9 |
| Liver | n=10 | n=10 | n=9 | n=8 | n=9 |
| Not remarkable | 10 | 7 | 9 | 4 | 0 |
| Dark | 0 | 0 | 0 | 2 | 9 |
| Prominent vessels | 0 | 0 | 0 | 0 | 0 |
| Enlarged | 0 | 0 | 0 | 0 | 9 |
| Pale focus (I)/area(s) | 0 | 1 | 0 | 1 | 0 |
| Dark focus (I)/area(s) | 0 | 0 | 0 | 0 | 0 |
| Mottled | 0 | 0 | 0 | 1 | 1 |
| Raised area(s) | 0 | 1 | 0 | 0 | 0 |
| Small mass(es) | 0 | 1 | 0 | 0 | 0 |
| Irregularly shaped | 0 | 0 | 0 | 0 | 0 |
| Firm | 0 | 0 | 0 | 0 | 0 |
| H-irregularly shaped | 0 | 0 | 0 | 0 | 0 |

Table C.3.2.15. Gross Pathological Examination of Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| Terminal Sacrifice | | | | | |
| Testes | n=41 | n=38 | n=40 | n=33 | n=27 |
| Not remarkable | 36 | 35 | 38 | 33 | 24 |
| Dark | 1 | 0 | 0 | 0 | 0 |
| Unequal size | 2 | 0 | 2 | 0 | 0 |
| Soft (flaccid) | 0 | 1 | 0 | 0 | 2 |
| Small | 0 | 1 | 0 | 0 | 2 |
| Dark/pale material | 1 | 1 | 0 | 0 | 1 |
| H-unequal size | 2 | 1 | 1 | 0 | 0 |
| Epididymides | n=41 | n=38 | n=40 | n=33 | n=27 |
| Not remarkable | 41 | 38 | 40 | 32 | 27 |
| Pale focus (I)/area(s) | 0 | 0 | 0 | 1 | 0 |
| Liver | n=41 | n=38 | n=40 | n=33 | n=27 |
| Not remarkable | 31 | 31 | 30 | 14 | 0 |
| Dark | 1 | 0 | 2 | 14 | 26 |
| Enlarged | 0 | 0 | 1 | 0 | 17 |
| Pale | 0 | 0 | 0 | 0 | 0 |
| Pale focus (I)/area(s) | 2 | 1 | 0 | 3 | 2 |
| Dark focus (I)/area(s) | 2 | 0 | 0 | 0 | 0 |
| Mottled | 0 | 0 | 0 | 0 | 1 |
| Raised area(s) | 2 | 0 | 1 | 2 | 1 |
| Small mass(es) | 2 | 3 | 4 | 2 | 5 |
| Irregularly shaped | 0 | 0 | 0 | 0 | 1 |
| Mass(es) | 1 | 3 | 2 | 1 | 3 |
| Cyst(s) | 0 | 0 | 0 | 1 | 0 |
| Small | 0 | 0 | 0 | 0 | 0 |
| H-small mass(es) | 0 | 0 | 0 | 0 | 1 |
| H-cyst(s) | 0 | 0 | 0 | 1 | 0 |
| H-pale focus (I)/area(s) | 0 | 0 | 0 | 0 | 0 |
| H-raised area(s) | 0 | 0 | 0 | 0 | 0 |

Organ weights were significantly affected by treatment at each of the timepoints assessed, but an effect on testis weight was observed only at terminal sacrifice when animals had completed 78 weeks of treatment. After 26 weeks of treatment, absolute and relative liver weights were increased in male mice receiving 80 and 320 ppm quizalofop-ethyl. After 52 weeks of treatment, absolute and relative liver weights were again increased in male mice receiving 80 and 320 ppm quizalofop-ethyl, while absolute kidney weight was increased in the 320 ppm animals, and relative kidney weight was

increased in the 80 ppm animals. After 78 weeks of treatment, absolute and relative liver weights were again increased in male mice receiving 80 and 320 ppm quizalofop-ethyl, and both absolute and relative adrenal weights were increase in animals in the 10, 80 and 320 ppm groups. At this terminal sacrifice, both absolute and relative testes weights were significantly decreased in mice receiving 320 ppm quizalofop-ethyl.

Table C.3.2.16. Absolute Organ Weights for Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | n=10 | n=10 | n=9 | n=9 | n=10 |
| Terminal Body Weight (g) ± S.D. | 31.5±2.3 | 31.4±3.7 | 31.0±2.6 | 30.9±2.2 | 30.5±3.9 |
| Mean Testes Weight (g) ± S.D. | 0.35±0.02 | 0.39±0.07 | 0.37±0.04 | 0.40±0.05 | 0.36±0.05 |
| Mean Liver Weight (g) ± S.D. | 1.34±0.08 | 1.39±0.26 | 1.34±0.12 | 1.54*±0.12 | 2.48*±0.28 |
| Mean Kidneys Weight (g) ± S.D. | 0.58±0.07 | 0.58±0.09 | 0.57±0.07 | 0.56±0.06 | 0.57±0.08 |
| 52 Week Interim Sacrifice | n=10 | n=10 | n=9 | n=8 | n=9 |
| Terminal Body Weight (g) ± S.D. | 32.1±2.7 | 32.2±2.1 | 31.7±2.0 | 30.0±3.2 | 32.6±1.9 |
| Mean Testes Weight (g) ± S.D. | 0.39±0.05 | 0.36±0.04 | 0.36±0.06 | 0.37±0.05 | 0.39±0.05 |
| Mean Liver Weight (g) ± S.D. | 1.27±0.14 | 1.43±0.27 | 1.33±0.12 | 1.56*±0.19 | 2.47*±0.18 |
| Mean Kidneys Weight (g) ± S.D. | 0.56±0.05 | 0.59±0.02 | 0.63±0.09 | 0.58±0.06 | 0.64*±0.04 |
| Terminal Sacrifice | n=41 | n=38 | n=40 | n=33 | n=27 |
| Terminal Body Weight (g) ± S.D. | 33.1±3.5 | 31.9±2.9 | 32.5±3.2 | 32.6±3.8 | 31.9±3.1 |
| Mean Testes Weight (g) ± S.D. | 0.40±0.12 | 0.40±0.06 | 0.39±0.07 | 0.39±0.06 | 0.34*±0.07 |
| Mean Liver Weight (g) ± S.D. | 1.65±0.43 | 1.48±0.19 | 1.56±0.24 | 1.70±0.26 | 2.71*±0.61 |
| Mean Kidneys Weight (g) ± S.D. | 0.65±0.08 | 0.65±0.07 | 0.66±0.09 | 0.64±0.08 | 0.65±0.09 |
| Mean Adrenals Weight (g) ± S.D. | 0.004 ±0.002 | 0.003 ±0.001 | 0.005* ±0.001 | 0.006* ±0.001 | 0.007* ±0.002 |

** p<0.05 (statistical test not specified)*

Table C.3.2.17. Relative Organ Weights for Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks – Organ/Terminal Bodyweight Ratio (%) (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | n=10 | n=10 | n=9 | n=9 | n=10 |
| Testes (mean ± S.D.) | 1.111±0.110 | 1.249±0.199 | 1.191±0.165 | 1.306±0.178 | 1.183±0.184 |
| Liver (mean ± S.D.) | 4.273±0.307 | 4.415±0.374 | 4.334±0.292 | 4.938*±0.298 | 8.186*±0.873 |
| Kidneys (mean ± S.D.) | 1.856±0.211 | 1.834±0.126 | 1.846±0.146 | 1.801±0.199 | 1.895±0.309 |
| 52 Week Interim Sacrifice | n=10 | n=10 | n=9 | n=8 | n=9 |
| Testes (mean ± S.D.) | 1.205±0.160 | 1.106±0.094 | 1.151±0.195 | 1.255±0.148 | 1.191±0.141 |
| Liver (mean ± S.D.) | 3.964±0.285 | 4.406±0.594 | 4.199±0.240 | 5.211*±0.406 | 7.588*±0.614 |
| Kidneys (mean ± S.D.) | 1.748±0.134 | 1.826±0.138 | 2.001*±0.146 | 1.947±0.230 | 1. 958±0.185 |
| Terminal Sacrifice | n=41 | n=38 | n=40 | n=33 | n=27 |
| Testes (mean ± S.D.) | 1.220±0.349 | 1.252±0.156 | 1.221±0.217 | 1.199±0.176 | 1.071*±0.188 |
| Liver (mean ± S.D.) | 5.035±1.492 | 4.658±0.647 | 4.811±0.741 | 5.230±0.758 | 8.489±1.959 |
| Kidneys (mean ± S.D.) | 1.971±0.257 | 2.054±0.201 | 2.033±0.282 | 1.965±0.194 | 2. 040±0.259 |
| Adrenals (mean ± S.D.) | 0.012±0.005 | 0.011±0.003 | 0.016*±0.004 | 0.019*±0.004 | 0. 023*±0.008 |

** $p<0.05$ (statistical test not specified)*

Compound-related changes in liver of male mice treated with 320 ppm quizalofop-ethyl were observed following histopathological examination at sacrifice after 26, 52 and 78 weeks of treatment, and were also observed in animals that died during the course of treatment. The changes included diffuse hepatocytic enlargement, hepatocytic pigmentation, sinusoidal cell pigmentation and focal pigmented macrophages. There was also some indication of effects on livers of animals treated with 80 ppm quizalofop-ethyl, but these effects were less well defined. Effects on the testes were observed in the animals sacrificed after 78 weeks of treatment, combined for analysis with those that died other than at scheduled sacrifice. The incidence and severity of bilateral testicular atrophy was considered to be increased in the 80 and 320 ppm animals, with the

incidence in the 320 ppm group being statistically significant (p=0.01142, Fisher's Exact Test).

Table C.3.2.18. Histopathological Examination of Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 26 Week Interim Sacrifice | | | | | |
| Testes | n=10 | n=10 | n=9 | n=9 | n=10 |
| Not remarkable | 10 | 9 | 8 | 9 | 8 |
| Abnormal sperm forms, bilateral | 0 | 1 | 0 | 0 | 1 |
| Atrophy, unilateral | 0 | 0 | 1 | 0 | 0 |
| Hemorrhage/congestion | 0 | 0 | 0 | 0 | 1 |
| Epididymides | n=10 | n=10 | n=9 | n=9 | n=10 |
| Not remarkable | 9 | 9 | 8 | 9 | 10 |
| Mononuclear infiltration | 1 | 1 | 1 | 0 | 0 |
| Liver | n=10 | n=10 | n=9 | n=9 | n=10 |
| Not remarkable | 2 | 2 | 3 | 1 | 0 |
| B-hepatocellular adenoma | 0 | 0 | 1 | 0 | 0 |
| Diffuse hepatocytic enlargement | 0 | 0 | 0 | 0 | 10 |
| Centrolobular hepatocytic enlargement | 0 | 1 | 0 | 1 | 0 |
| Hepatocytic pigmentation | 0 | 0 | 0 | 0 | 10 |
| Sinusoidal cell pigmentation | 0 | 0 | 0 | 0 | 9 |
| Focal mononuclear infiltration | 5 | 7 | 5 | 5 | 3 |
| Focal hepatitis | 5 | 2 | 2 | 4 | 3 |
| Bile duct hyperplasia | 2 | 0 | 0 | 0 | 1 |
| Coagulative necrosis | 0 | 2 | 1 | 0 | 1 |
| Hepatocytic vacuolization | 0 | 0 | 1 | 1 | 0 |
| Extramedullary hematopoiesis | 0 | 0 | 1 | 0 | 0 |
| Chronic infarct | 0 | 0 | 0 | 0 | 0 |
| Megakaryocytes within sinusoids | 0 | 0 | 0 | 0 | 0 |
| Mineralization | 0 | 0 | 0 | 0 | 0 |

Table C.3.2.18. Histopathological Examination of Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| 52 Week Interim Sacrifice | | | | | |
| Testes | n=10 | n=10 | n=9 | n=8 | n=9 |
| Not remarkable | 10 | 9 | 8 | 8 | 7 |
| Interstitial cell hyperplasia | 0 | 0 | 0 | 0 | 1 |
| Abnormal sperm forms, unilateral | 0 | 0 | 0 | 0 | 1 |
| Abnormal sperm forms, bilateral | 0 | 1 | 0 | 0 | 0 |
| Atrophy, unilateral | 0 | 0 | 0 | 0 | 1 |
| Atrophy, bilateral | 0 | 0 | 1 | 0 | 0 |
| Sperm stasis | 0 | 0 | 0 | 0 | 1 |
| Epididymides | n=10 | n=10 | n=9 | n=8 | n=9 |
| Not remarkable | 10 | 10 | 8 | 8 | 8 |
| Mononuclear infiltration | 0 | 0 | 1 | 0 | 0 |
| Decreased sperm | 0 | 0 | 0 | 0 | 1 |
| Abnormal sperm forms, unilateral | 0 | 0 | 0 | 0 | 1 |
| Liver | n=10 | n=10 | n=9 | n=8 | n=9 |
| Not remarkable | 1 | 0 | 2 | 0 | 0 |
| B-hepatocellular adenoma | 0 | 2 | 0 | 1 | 0 |
| M-hemangiosarcoma | 0 | 1 | 0 | 0 | 0 |
| Focus (I) of cell alteration | 0 | 1 | 0 | 1 | 1 |
| Diffuse hepatocytic enlargement | 0 | 0 | 0 | 0 | 9 |
| Centrolobular hepatocytic enlargement | 0 | 1 | 0 | 1 | 0 |
| Hepatocytic pigmentation | 0 | 0 | 0 | 3 | 9 |
| Sinusoidal cell pigmentation | 1 | 0 | 0 | 3 | 9 |
| Focal pigmented macrophages | 0 | 2 | 4 | 3 | 9 |
| Amyloid | 0 | 0 | 0 | 0 | 0 |
| Focal mononuclear infiltration | 5 | 4 | 5 | 2 | 8 |
| Focal hepatitis | 5 | 6 | 6 | 5 | 5 |
| Bile duct hyperplasia | 0 | 0 | 1 | 0 | 3 |
| Coagulative necrosis | 0 | 1 | 0 | 1 | 2 |
| Hepatocytic vacuolization | 1 | 0 | 0 | 0 | 1 |
| Extramedullary hematopoiesis | 0 | 2 | 0 | 0 | 0 |
| Chronic infarct | 0 | 0 | 0 | 0 | 0 |
| Hepatocellular cytoplasmic clearing | 0 | 0 | 0 | 0 | 3 |
| Bile duct ectasia | 1 | 0 | 0 | 0 | 0 |
| Fibrosis | 0 | 0 | 1 | 0 | 0 |
| Vascular congestion | 0 | 0 | 0 | 0 | 0 |

Table C.3.2.18. Histopathological Examination of Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| Terminal Sacrifice | | | | | |
| Testes | n=41 | n=38 | n=40 | n=33 | n=27 |
| Not remarkable | 25 | 20 | 16 | 11 | 11 |
| Interstitial cell tumor | 1 | 0 | 0 | 0 | 0 |
| Interstitial cell hyperplasia | 2 | 0 | 0 | 2 | 2 |
| Abnormal sperm forms, unilateral | 2 | 0 | 1 | 0 | 1 |
| Abnormal sperm forms, bilateral | 0 | 1 | 1 | 1 | 0 |
| Atrophy, unilateral | 6 | 13 | 15 | 10 | 5 |
| Atrophy, bilateral | 4 | 3 | 5 | 8 | 9 |
| Sperm stasis | 5 | 4 | 11 | 5 | 3 |
| Degeneration/necrosis, unilateral | 0 | 0 | 1 | 0 | 0 |
| Mineralization | 2 | 2 | 1 | 0 | 1 |
| Amyloid | 5 | 2 | 1 | 3 | 3 |
| Vasculitis | 0 | 1 | 0 | 0 | 2 |
| Epididymides | n=41 | n=38 | n=40 | n=33 | n=27 |
| Not remarkable | 27 | 26 | 19 | 23 | 14 |
| Mononuclear infiltration | 3 | 3 | 6 | 2 | 2 |
| Decreased sperm | 5 | 5 | 4 | 2 | 5 |
| Abnormal sperm forms, unilateral | 0 | 2 | 6 | 1 | 3 |
| Abnormal sperm forms, unilateral | 8 | 5 | 6 | 5 | 6 |
| Tubular dilation | 0 | 2 | 2 | 0 | 3 |
| Fibrosis | 0 | 1 | 0 | 0 | 1 |
| Sperm granuloma | 0 | 0 | 2 | 2 | 0 |
| Tubular atrophy | 0 | 0 | 1 | 0 | 0 |

Table C.3.2.18. Histopathological Examination of Male Mice Exposed to Quizalofop-Ethyl in Diet for 78 Weeks (Nissan Chemical Industries, Ltd., 1985f) (continued).

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | 0 ppm (control) | 2 ppm | 10 ppm | 80 ppm | 320 ppm |
| Terminal Sacrifice | | | | | |
| Liver | n=41 | n=38 | n=40 | n=33 | n=27 |
| Not remarkable | 1 | 8 | 6 | 1 | 0 |
| M-hepatocellular carcinoma | 3 | 4 | 2 | 1 | 6 |
| B-hepatocellular adenoma | 3 | 4 | 5 | 5 | 6 |
| M-hemangiosarcoma | 0 | 0 | 0 | 1 | 0 |
| B-hemangioma | 0 | 0 | 0 | 0 | 0 |
| N-hemangiosarcoma | 1 | 0 | 0 | 0 | 0 |
| X-malignant lymphoma | 3 | 0 | 0 | 0 | 0 |
| Focus (I) of cell alteration | 0 | 0 | 2 | 1 | 0 |
| Areas (S) of cell alteration | 2 | 0 | 0 | 1 | 1 |
| Focal hyperplasia | 0 | 0 | 0 | 1 | 3 |
| Diffuse hepatocytic enlargement | 0 | 0 | 0 | 1 | 27 |
| Centrolobular hepatocytic enlargement | 5 | 2 | 1 | 4 | 0 |
| Hepatocytic pigmentation | 0 | 0 | 1 | 18 | 26 |
| Sinusoidal cell pigmentation | 4 | 4 | 2 | 13 | 27 |
| Focal pigmented macrophages | 6 | 12 | 8 | 13 | 24 |
| Amyloid | 6 | 2 | 1 | 1 | 10 |
| Focal mononuclear infiltration | 25 | 22 | 20 | 21 | 23 |
| Focal hepatitis | 21 | 28 | 12 | 19 | 15 |
| Bile duct hyperplasia | 0 | 1 | 1 | 0 | 2 |
| Coagulative necrosis | 3 | 2 | 8 | 5 | 2 |
| Hepatocytic vacuolization | 0 | 0 | 2 | 0 | 1 |
| Extramedullary hematopoiesis | 4 | 0 | 3 | 1 | 1 |
| Chronic infarct | 0 | 0 | 0 | 0 | 1 |
| Centrolobular hepatocytic vacuolation | 1 | 2 | 3 | 1 | 0 |
| Hemorrhage | 0 | 0 | 0 | 0 | 0 |
| Sinusoidal cell hyperplasia | 2 | 0 | 0 | 0 | 0 |
| Mineralization | 1 | 1 | 2 | 0 | 0 |
| Bile duct ectasia | 1 | 0 | 0 | 1 | 1 |
| Fibrosis | 2 | 0 | 0 | 0 | 0 |
| Vascular congestion | 1 | 0 | 1 | 0 | 0 |
| Necrosis of individual hepatocytes | 0 | 2 | 1 | 0 | 0 |
| Individual megacytic hepatocytes | 1 | 1 | 1 | 0 | 0 |
| Focal hypertrophy of hepatocytes | 0 | 0 | 0 | 2 | 0 |

**Nippon Experimental Medical Research Institute, 1983b**. Pregnant rats of strain Jcl:SD aged 10-12 weeks at the beginning of the experiment were administered quizalofop-ethyl by oral gavage on days 6-15 of gestation, at dose levels of 0 (control), 30, 100 or 300 mg/kg/day, as described in Section C.1.2.

The two male and two female pups from each litter were used in a test of reproductive ability at age 10 weeks. Male and female pairs were established within treatment groups, with sibling pairs being avoided. Pairs were co-housed for 10 days for breeding. If the female did not become pregnant, breeding was repeated as follows. For the male, an untreated multiparous female was added to the pair for 10 days; if the male failed to mate or induce pregnancy in one of the females, he was paired with two different females for another 10 days. The female from the original pair was paired for 10 days with a male which had proven reproductive ability from the same treatment group. If no such male was available, the female was paired with an untreated male of proven breeding ability. If pregnancy did not result, the process was repeated for a further 10 days with a different male. The results of the test of reproductive ability are summarized in Table C.1.2.17. There were no significant differences in reproductive ability between the control and any of the treatment groups.

### *C.3.3 Other Relevant Data*

The general pharmacokinetics of quizalofop-ethyl in rats are described in section B.4. Quizalofop-ethyl is absorbed to a considerable extent after oral administration. Peak plasma or blood levels occur six to nine hours after administration, with decay around 20 to 30 hours. Quizalofop-ethyl and/or its metabolites are distributed to all tissues tested, including testis and epididymis (see Table B.4.2.2). Concentrations in testes and epididymis were in the middle of the range of tissues tested, indicating no excess accumulation nor protection.

### *C.3.4 Integrative Evaluation*

Testicular atrophy has been reported in three studies, one each in dog, rat and mouse chronically or subchronically exposed to quizalofop-ethyl in diet. Another study in dogs and another study in rats failed to show evidence of testicular effects. The study parameters and outcomes are summarized in Table C.3.4.1. Where parameters were assessed at more than one timepoint, the values at the end of the treatment period are summarized.

In the case of the dog studies, the first study conducted (Nippon Experimental Medical Research Institute, 1982) reported a histopathological finding of testicular atrophy following 26 weeks exposure to 400 ppm quizalofop-ethyl in diet. This effect occurred in two males; it is not clear from the study report how many animals in this group were examined (although it is unlikely that more than three of the six males in the group were). The severity of the effect was such that spermatogenesis was not impaired, and effects on several other organs and tissues were also noted at this dose level. The second dog study

(Nissan Chemical Industries, Ltd., 1985d) paralleled the first in all respects except duration of exposure. After 56 weeks exposure, no testicular atrophy was observed in male dogs exposed to 400 ppm quizalofop-ethyl in diet (n=6).

A study in Sprague-Dawley rats exposed to levels of up to 1280 ppm quizalofop-ethyl in diet demonstrated a high incidence of testicular atrophy at the end of the 13 week treatment period (Nissan Chemical Industries, Ltd., 1982). Testicular atrophy at this level of exposure was also apparent after a six week recovery period. Food intake over the treatment period was significantly lower in these animals than in controls, and concurrent manifestations of toxicity included effects on liver and blood. Another study in Sprague-Dawley rats exposed to lower concentrations of quizalofop-ethyl for a much longer period, 400 ppm for 104 weeks, did not show any evidence of testicular atrophy (Nissan Chemical Industries, Ltd., 1985e).

The only study in mice reviewed also showed evidence of effect on the testes, with bilateral testicular atrophy being reported after exposure for 78 weeks to concentrations of 80 or 320 ppm quizalofop-ethyl in diet (Nissan Chemical Industries, Ltd., 1985f). The effect was more pronounced at the higher concentration.

In all cases where testicular atrophy was reported, other manifestations of toxicity such as effects on liver weight and condition were also reported. There was no discussion of possible causal relationship between the various manifestations of systemic toxicity and testicular effects in any of the studies reviewed.

The only available study in which reproductive capability of animals exposed to quizalofop-ethyl was assessed was a study in rats exposed developmentally via administration of quizalofop-ethyl to their dams on days 6-15 of gestation (Nippon Experimental Medical Research Institute, 1983b). Animals were bred at age 10 weeks. No effects on reproductive parameters or pregnancy outcome were observed following maternal exposures of up to 300 mg/kg/day.

Table C.3.4.1. Summary of Reported Effects on Testes

| Species | Dose Levels | Duration/ Period of Exposure | Effect on Testicular Weight (% control weight) | Effect on Gross Testicular Morphology | Effect on Testicular Histopathology | Study |
|---|---|---|---|---|---|---|
| Dog (Beagle) (n=6) | 0, 25, 100, 400 ppm (diet) [0, 0.79, 3.20, 12.75 mg/kg/ day] | 26 weeks (age 7-13 months) | 25ppm: 112%<br>100: 108%<br>400: 115% | Not assessed | Atrophy of testis in 2 animals of 400 ppm group | NEMRI, 1982 |
| Dog (Beagle) (n=6) | 0, 25, 100, 400 ppm (diet) | 52 weeks (age 7-19 months) | 25ppm: 88%<br>100: 90%<br>400: 87% | No apparent effect | No apparent effect | NCI, 1985d |
| Rat (Sprague-Dawley) (n=15) | 0, 40, 128, 1280 ppm (diet) [0, 2.6, 8.4, 82.9 mg/kg/ day] | 13 weeks (age 5-18 weeks) | 40ppm: 106%<br>128: 102%<br>1280: 68%*[1] | 12/15<br>1280 ppm animals had small testes, 4/15<br>1280 ppm animals had flaccid testes | 13/15<br>1280 ppm animals had testicular atrophy and/or suppressed spermato-genesis | NCI, 1982 |
| Rat (Sprague-Dawley) (n=50) | 0, 25, 100, 400 ppm (diet) [0, 0.9, 3.7, 15.5 mg/kg/ day] | 104 weeks (age 5-109 weeks) | 25ppm: 87%<br>100: 103%<br>400: 93% | No apparent effect | No apparent effect | NCI, 1985e |

Table C.3.4.1. Summary of Reported Effects on Testes (continued).

| Species | Dose Levels | Duration/ Period of Exposure | Effect on Testicular Weight (% control weight) | Effect on Gross Testicular Morphology | Effect on Testicular Histopathology | Study |
|---|---|---|---|---|---|---|
| Mouse (CD-1) (n=50) | 0, 2, 10, 80, 320 ppm (diet) [0, N/R[3], 1.55, N/R, 49.77 mg/kg/ day] | 78 weeks (age 6-84 weeks) | 2ppm: 100%<br>10: 98%<br>80: 98%<br>320: 85%*[2] | No apparent effect | Increased incidence and severity of bilateral testicular atrophy in 80 and 320 ppm animals | NCI, 1985f |

** statistically significantly different from control value.*
*[1] statistically significant decreases reported at 26 and 78 week interim sacrifices, but not at 52 week interim or 105 week terminal sacrifices (terminal values shown).*
*[2] no statistically significant changes reported at 26 and 52 week interim sacrifices (terminal values shown).*
*[3] not included in study report.*

**SUMMARY**

## D.1. Developmental Toxicity

Two studies of the potential effects of quizalofop-ethyl on development were reviewed, one conducted in rabbits (Nippon Experimental Medical Research Institute, 1983a) and the other conducted in rats (Nippon Experimental Medical Research Institute, 1983b). In both studies, quizalofop-ethyl was administered to pregnant females during the period of organogenesis for the species in question.

In the rabbit study (Nippon Experimental Medical Research Institute, 1983a), the highest dose tested (60 mg/kg/day) induced mild toxicity in the dams, but resulted in no apparent treatment-related adverse effects in the fetuses other than an increase in the proportion of female fetuses in the 30 mg/kg dose group, the second-highest dose tested.

The rat study (Nippon Experimental Medical Research Institute, 1983b) included both an evaluation of fetal effects at the end of the gestational period and postnatal evaluation of young that were delivered and suckled by their dams. There was a statistically significant decrease in the number of fetuses alive at the time of sacrifice of the dams on day 21 of

gestation in the high dose group receiving 300 mg/kg/day quizalofop-ethyl, and a significant increase in the number of animals with retained placenta in the same group. The incidence of fetuses in the high dose (300 mg/kg/day) group showing skeletal variations was significantly higher than the control level, as was the number of fetuses showing bilateral and total incidence of $14^{th}$ ribs. There was also a significant increase in the incidence of bilateral $14^{th}$ ribs in fetuses of the 100 mg/kg/day dose group.

The only statistically significant difference between control and treated offspring at parturition was a higher proportion of male pups in the 300 mg/kg/day group. Postnatal bodyweight in both male and female pups in the 300 mg/kg/day group was significantly lower than control values both pre and post-weaning, and food intake by these animals was also significantly lower than control values. Uterine weights in offspring assessed at age 8 weeks were significantly lower in offspring of 300mg/kg/day dams than in offspring of controls.

There were no apparent effects on developmental landmarks such as incisor budding, hair eruption, descent of testicles or vaginal opening. Assessment of various behavioral indices also revealed no significant differences between treated and control animals. Breeding of male and female offspring at age 10 weeks did not show any differences between control and treated animals in reproductive parameters or in fetal development.

## D.2. Female Reproductive Toxicity

Female reproductive toxicity was investigated in a 26 week and a 52 week feeding study in dogs, a 90 day and a two year feeding study in rats and an 18 month feeding study in mice. Reproductive capability was also investigated in rats exposed to quizalofop-ethyl *in utero*.

Evaluations of gross pathology and histopathology did not reveal any effects on ovaries or uterus in either the first dog study (Nippon Experimental Medical Research Institute, 1982) or the second dog study (Nissan Chemical Industries, Ltd., 1985d). Ovarian weights varied from control values in both studies, but there was no apparent dose-response relationship and the effects were not reported to be statistically significant. Uterine weights were reported only in the first study (Nippon Experimental Medical Research Institute, 1982). While they varied markedly from control values, there was again no apparent dose-response relationship and the effects were not reported to be statistically significant.

Two studies in Sprague-Dawley rats, one in which the animals were exposed to levels of up to 1280 ppm quizalofop-ethyl in diet for 13 weeks (Nissan Chemical Industries, Ltd., 1982) and another in which the animals were exposed to lower concentrations for a much longer period, up to 400 ppm for 104 weeks, did not show any evidence of effects on female reproductive organs (Nissan Chemical Industries, Ltd., 1985e).

The only study in mice reviewed showed significantly increased ovarian weights at all dose levels. This effect was statistically significant for all dose groups after 78 weeks of

exposure to quizalofop-ethyl, and there was also a non-significant increase in ovarian weight in all groups at interim sacrifice following 52 weeks of exposure. There was no clear evidence of other effects on the ovaries or uterus, although there was an increase in the incidence of ovarian hemorrhage after 78 weeks of exposure at the highest dose tested (Nissan Chemical Industries, Ltd., 1985f).

No effects on reproductive capability of animals exposed to quizalofop-ethyl was reported in a study in rats exposed developmentally via administration of quizalofop-ethyl to their dams on days 6-15 of gestation (Nippon Experimental Medical Research Institute, 1983b).

## D.3. Male Reproductive Toxicity

Male reproductive toxicity was investigated in a 26 week and a 52 week feeding study in dogs, a 90 day and a two year feeding study in rats and an 18 month feeding study in mice. Reproductive capability was also investigated in rats exposed to quizalofop-ethyl *in utero*.

Testicular atrophy was reported in three studies, one each in dog, rat and mouse chronically or subchronically exposed to quizalofop-ethyl in diet. Another study in dogs and another study in rats failed to show evidence of testicular effects. In the case of the dog studies, the first study conducted (Nippon Experimental Medical Research Institute, 1982) reported a histopathological finding of testicular atrophy in two males following 26 weeks exposure to 400 ppm quizalofop-ethyl in diet. The severity of the effect was such that spermatogenesis was not impaired, and effects on several other organs and tissues were also noted at this dose level. The second dog study (Nissan Chemical Industries, Ltd., 1985d) paralleled the first in all respects except duration of exposure. After 56 weeks exposure, no testicular atrophy was observed in male dogs exposed to 400 ppm quizalofop-ethyl in diet.

A study in Sprague-Dawley rats exposed to levels of up to 1280 ppm quizalofop-ethyl in diet demonstrated a high incidence of testicular atrophy at the end of the 13 week treatment period (Nissan Chemical Industries, Ltd., 1982). Testicular atrophy at this level of exposure was also apparent after a six week recovery period. Another study in Sprague-Dawley rats exposed to lower concentrations of quizalofop-ethyl for a much longer period, 400 ppm for 104 weeks, did not show any evidence of testicular atrophy (Nissan Chemical Industries, Ltd., 1985e).

The only study in mice reviewed also showed evidence of effect on the testes, with bilateral testicular atrophy being reported after exposure for 78 weeks to concentrations of 80 or 320 ppm quizalofop-ethyl in diet (Nissan Chemical Industries, Ltd., 1985f). The effect was more pronounced at the higher concentration.

No effects on reproductive capability of animals exposed to quizalofop-ethyl was reported in a study in rats exposed developmentally via administration of quizalofop-

ethyl to their dams on days 6-15 of gestation (Nippon Experimental Medical Research Institute, 1983b).

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