Summary of Toxicity Studies with Pyridaben

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DESCRIPTION OF PYRIDABEN

Pyridaben, a pyridazinone derivative, is a new acaricide and insecticide discovered by Nissan Chemical Industries, Ltd. for control of mites and some insects such as white flies, aphids and thrips. Pyridaben has been developed for application to fruits as a 20% wettable powder (WP) and for vegetables, tea and ornamentals as a 20% suspension concentrate (SC) in Japan. Technical information given in this summary was used to register pyridaben as Sanmite® in Japan.

Pyridaben has the following chemical and physical properties.

- **Common name:** Pyridaben
- **Code No.:** NC-129, NCI-129
- **Chemical name:** 2-tert-Butyl-5-(4-tert-butyl-benzylthio)-4-chloropyridazin-3(2H)-one
- **Chemical structure:**

  ![Chemical Structure](image)

  Molecular formula: C₁₉H₂₅C₁N₂OS
- **Molecular weight:** 364.9
- **Physical state:** White crystalline solid
- **Specific gravity:** d³ 1.2
- **Melting point:** 111-112°C
- **Vapor pressure:** 1.9 × 10⁻⁶ mmHg (20°C)
- **Solubility (g/l, 20°C):** Water, 1.2 × 10⁻⁵; acetone, 460; acetonitrile, 69; ethyl acetate, 400; dichloromethane, 1530; n-hexane, 10
- **Partition coefficient (n-octanol/water):** log Pₐw = 6.37 (23°C)
- **Stability:** In water, stable at pH 4-9; to heat, no decomposition at 50°C for 3 months; to light, relatively unstable; in organic solvents, stable in most organic solvents.

ACUTE TOXICITY STUDIES

Pyridaben has been studied for acute toxicity in different species and via various routes. The median lethal doses are summarized in Table 1 and the results show pyridaben to be of moderate to low toxicity. No mortality occurred and there were minimal signs seen in percutaneous tests. On the other hand, mortality occurred most frequently within 1 day of dosing in oral and intraperitoneal tests. Major clinical signs observed were decreased spontaneous motor activity, abnormal gait, prone/recumbent posture, arched back posture, eye closing, piloerection and bradypnea. The surviving animals rapidly returned to normality. In the inhalation test, there were mortalities within 1 day after exposure and clinical signs were also reversible in surviving animals.

PRIMARY DERMAL IRRITATION STUDY

The potential of pyridaben to cause inflammatory or corrosive changes upon first contact with skin was assessed by semi-occluded application of 0.5 g of the test material to the shaved dorsa of 6 female New Zealand White rabbits for 4 hr. Dermal reactions were assessed 1, 24, 48 and 72 hr after removal of the dressings, according to the method of Draize. No dermal irritation responses were observed in any animal at any time during the 72 hr observation period. Pyridaben was classified as non-irritant to skin.

(PRIMARY EYE IRRITATION STUDY)

The potential of pyridaben to cause damage to conjunctivae, iris or cornea was assessed in...
6 female New Zealand White rabbits, each subject to a single ocular instillation of 0.1 g of test material. Ocular reactions were examined 1, 24, 48 and 72 hr after treatment, according to the modified method of Draize. A well defined or slight injection of the conjunctival blood vessels and a slight chemosis and ocular discharge were observed. These signs of mild irritation disappeared 72 hr after treatment. Ocular effects were largely confined to slight reversible conjunctivitis and pyridaben can be considered to be non-irritant to the eye.

(Life Science Research, Ltd., 1986)

DERMAL SENSITIZATION STUDIES

1. Maximization Test

The sensitizing potential of pyridaben was evaluated in accordance with Magnusson and Kligman method using female Dunkin-Hartley guinea pigs. Induction doses of pyridaben mixed with prepared Freund's Complete Adjuvant (FCA/sterile water), as well as the test substance in peanut oil and the prepared FCA alone, were injected intradermally on day zero in the clipped shoulder region of 20 female Dunkin-Hartley guinea pigs. The concentration of the test substance was 5% w/v. A negative vehicle control group of 20 animals was treated in the same manner as the test group, except no test substance was administered. A closed patch topical application dose of 25% w/w test substance in petrolatum or petrolatum alone was applied to the re-clipped same shoulder area on day 7. The exposure period was 48 hr. On day 21, all test and negative control animals were challenged by 24 hr occluded topical application of 2.5% w/w pyridaben in petrolatum and petrolatum alone to the clipped flank. Dermal responses to the challenge procedure were assessed 24, 48 and 72 hr after challenge patch removal. There were no positive signs of erythema (i.e., score ≥1) and no edema observed at the test sites of any animal in the negative control or test substance group. Positive control test was conducted within 6 months of this study.

Pyridaben did not produce any skin reaction and can be considered to be non-sensitizing under the conditions of this test.

(International Research and Development Corporation, 1987)
2. Modified Buehler Test

The potential of pyridaben to cause delayed contact hypersensitivity in guinea pigs was assessed by a modified version of the method of Buehler. The shaven left flanks of 10 male and 10 female Dunkin-Hartley guinea pigs were subjected to 6 hr occluded topical application of 50% w/v pyridaben in paraffin oil on day 1, 8 and 15. On day 29, all test and control animals were challenged by 6 hr occluded topical application of 50 and 10% pyridaben in paraffin oil to the shaven right flank. Dinitrochlorobenzene (DNCB) was used as a positive control. Dermal responses to the challenge procedure were assessed approximately 24 and 48 hr after application of the occlusive dressings. Challenge application of 50 and 10% w/v pyridaben in paraffin oil caused a significant reaction (faint erythema or more marked response) in 2 control and 2 test animals. These changes were considered to reflect an irritation reaction rather than hypersensitivity response. Challenge application of 0.1% w/v DNCB caused a significant reaction in 5 of the 10 positive control animals. No response was observed in the irritation controls. It is concluded that, under conditions of this study, repeated occluded dermal applications of pyridaben did not cause delayed contact hypersensitivity in guinea pigs.

(Life Science Research, Ltd., 1990)

SUBACUTE AND SUBCHRONIC STUDIES

1. 13-Week Feeding Study in Rats

Pyridaben was administered continuously, via the diet, to groups of 10 male and 10 female CD rats at concentrations of 0, 30, 65, 155 or 350 ppm for 13 weeks. An additional 10 animals per sex were assigned to the highest and control groups for a 4-week reversibility period. There were no dosage-related clinical signs or mortality. There was a dosage-related effect on bodyweight gain, food consumption and food conversion efficiency in males and females receiving 155 or 350 ppm. In females receiving 65 ppm, the bodyweight gain and the efficiency of food conversion were also affected. Following withdrawal of treatment, the bodyweight gain and the efficiency of food conversion of animals which had previously received 350 ppm were significantly higher than in the respective control group. No evidence of toxicologically significant effects of treatment was noted at the ophthalmoscopic and haematological examinations. A number of changes were noted in blood chemistry parameters and organ weights in animals receiving 155 and 350 ppm, but these changes were considered to be secondary to the nutritional state and growth performance. No dosage-related microscopic changes were observed. The no-effect level was considered to be 30 ppm (equivalent to mean achieved dosages of 2.30 and 2.64 mg/kg/day, for males and females respectively).

(Life Science Research, Ltd., 1988)

2. 13-Week Feeding Study in Mice

Pyridaben was administered continuously, via the diet, to groups of 12 male and 12 female CD-1 mice at concentrations of 0, 30, 90, 270 or 810 ppm for 13 weeks. There were no dosage-related clinical signs or mortality. Lower bodyweight gain and food utilization efficiency were noted for males receiving 90 ppm or greater and for females receiving 270 or 810 ppm and at concentrations above 270 ppm food and water consumptions were reduced. Ophthalmoscopic examination revealed no evidence of response to treatment. At higher doses some haematological parameters were slightly affected and blood chemistry investigation revealed a number of differences between control and treated animals. These were considered to be associated with the effect on nutritional status at these dosages. In association with the marked effect on bodyweight, the bodyweight-relative liver weight was increased in animals receiving 270 or 810 ppm. This was not associated with any microscopic changes, and was not considered to be of toxicological significance. No-effect level was 30 ppm (equivalent to mean achieved dosages of 4.07 and 4.92 mg/kg/day for males and females respectively).

(Life Science Research, Ltd., 1988)

3. 13-Week Oral Study in Dogs

Pyridaben was administered orally in gelatin capsule to groups of 4 male and 4 female dogs at dosage levels of 0, 0.5, 1, 4 or 16 mg/kg/
day for 13 weeks. There were no effects on survival. Salivation was seen in some dogs at the upper 2 dose levels. Slight emesis was seen in several animals at 16 mg/kg/day and some females at 4 mg/kg/day. Decreased bodyweight gain was noted for males at the dose levels of 16 and 4 mg/kg/day; bodyweight loss was recorded for one animal in each of these groups. There was no dosage-related decrease in food consumption and there was no clear effect on food conversion efficiency. No changes were observed at ophthalmoscopic examination, and the results of haematology, blood chemistry and urinalysis showed no treatment-related effects. There were no test substance-related effects seen macroscopically, on organ weights or on microscopic examination. The no-effect level can be considered to be 1 mg/kg/day.

(International Research and Development Corporation, 1989)

4. 4-Week Inhalation Study in Rats
Pyridaben (92.6% active ingredient, 7.4% white carbon) was administered by inhalation as a respirable dust to groups of 5 male and 5 female CD rats at concentrations of 1, 3 or 10 mg/m³ under whole body exposure conditions. The exposure time was 6 hr per day, 5 days per week over a 4 weeks period. An additional 5 animals per sex were assigned to the highest and control groups for a 2-week reversibility period. There were no effects on survival. Clinical signs during exposure included a slight increase among the treated animals of dried red nasal discharge, and similar signs were noted after exposure at 3 and 10 mg/m³. These signs abated during the recovery period. Lower bodyweight gain and food consumption were recorded for animals exposed at the highest level but only during the first week of exposure. Haematology evaluations, no explanation for this effect was apparent. The no-effect level was considered to be 1 mg/m³.

(Bio-dynamics, 1989)

**CHRONIC TOXICITY AND ONCOGENICITY STUDIES**

1. 104-Week Feeding Study in Rats
Pyridaben was administered continuously, via the diet, to groups of 50 male and 50 female CD rats comprising the oncogenicity phase at concentrations of 4, 10, 28 or 80 ppm for 104 weeks. A further 35 male and 35 female rats were assigned to each of the groups treated at 4, 10 or 28 ppm, to the controls, and to an additional group which received 120 ppm. These animals comprised the toxicity phase. Each group in this toxicity phase was composed of 23 males and 23 females which were sacrificed after 53 weeks of treatment (interim sacrifice) and 12 males and 12 females which were sacrificed after 104 weeks of treatment (terminal sacrifice). These rats also provided blood and urine samples for clinical pathology investigation at 12, 23 and 50 weeks (interim animals), and at 76 and 104 weeks (terminal animals). The appearance and behaviour, mortality and cause of death of animals of the toxicity and oncogenicity phases were unaffected by treatment with pyridaben. Bodyweight gain and food consumption in rats which received 80 or 120 ppm were significantly lower than those of their controls. The efficiency of food conversion over the first 14 weeks of treatment was also reduced in the both sexes at 80 and 120 ppm. No evidence of treatment-related change was noted at the ophthalmoscopic, haematological, clinical chemical, macroscopic or microscopic investigations. There was no evidence of any oncogenic potential for pyridaben in this study. It was considered that the changes in rats receiving 80 or 120 ppm were toxicologically significant and that the maximum tolerated dosage level was therefore 80 ppm. A specific target organ was not, however, identified. The no-effect level was considered to be 28 ppm (equivalent to mean achieved dosages of approximately 1.1 and 1.5 mg/kg/day for males and females, respectively).

(Life Science Research, Ltd., 1990)
2. 78-Week Feeding Study in Mice

Pyridaben was administered continuously, via the diet, to groups of 32 male and 32 female CD-1 mice at concentrations of 2.5, 8, 25 or 80 ppm for 78 weeks. Another 12 animals per sex in each dose group were sacrificed after 53 weeks of treatment. The appearance and behaviour of animals were unaffected by treatment with pyridaben. A slightly higher incidence of mortality was noted in males which received 80 ppm than the controls. The overall bodyweight gain of mice which received 80 ppm was significantly lower than that of their controls. This was associated with the slightly low food consumption and reduced food utilization efficiency noted for these animals. A slight impairment in food utilization efficiency was also noted for males which received 25 ppm. Haematological investigations after 52 and 78 weeks of treatment revealed no changes that could be clearly related to treatment. Macroscopic examination and organ weights revealed no changes that could be clearly related to treatment. Microscopic examination revealed a low incidence of distended coagulation glands in males of the terminal phase which had received 80 ppm, when compared with the respective control. No evidence of any oncogenic potential of pyridaben was noted in this study. Evidence of treatment-related effects was noted in mice which received 25 or 80 ppm and the maximum tolerated dosage was considered to be within the range of these concentrations. A specific target organ was not, however, identified. The no effect level for mice was considered to be 8 ppm (equivalent to mean achieved dosages of 0.81 and 0.91 mg/kg/day for males and females).

(Life Science Research, Ltd., 1990)

3. 53-Week Oral Study in Dogs

Pyridaben was administered orally in gelatin capsule to groups of 4 male and 4 female dogs at dose levels of 0, 1, 4, 16 or 32 mg/kg/day for 1 year. There were no effects on survival. Salivation and emesis were seen in the treated groups, but the incidence was low and not considered to be related to treatment. Bodyweight gains in all treated groups were slightly lower than in the control group, but the differences from control were statistically significant. Individual animals receiving 4 mg/kg/day or greater showed thinness, but there was no clear relation to dosage. Food consumption and food conversion efficiency values were variable. There were no test substance-related effects on ophthalmoscopy. There were no apparent treatment related findings for haematology, blood chemistry or urinalysis values. Macroscopic changes were seen only in one female receiving 32 mg/kg/day and histopathological examination of the animal revealed hepatocellular hypertrophy. In conclusion, the bodyweight depression in the 1 mg/kg/day group was slight and this is considered to be the no adverse effect level.

(International Research and Development Corporation, 1990)

REPRODUCTIVE STUDY IN RATS

Pyridaben was administered continuously, via the diet, to groups of 25 male and 25 female CD rats at concentrations of 0, 10, 28 or 80 ppm throughout two successive generations. Both sexes (F0 generation) received 14 weeks treatment before pairing and 25 male and 25 female offspring were selected to form the F1 generation. F1 animals were also mated to produce F2 litters. The bodyweight gain of rats receiving 80 ppm was clearly reduced, although that of females showed a recovery during lactation. There was also a slight reduction in food consumption. Reproductive performance was unaffected. Necropsy of the F0 parents, F1 adults and F2 offspring revealed no macroscopic changes that were considered to be related to treatment. Although the weights of reproductive organs were slightly increased at 80 ppm, microscopic examination of the reproductive organs revealed no significant findings. The maximum tolerated level was 80 ppm. The no effect level was considered to be 28 ppm (equivalent to mean achieved dosages of 2.02 and 2.50 mg/kg/day for F0 males and females, respectively, and 2.37 and 2.80 mg/kg/day for F1 males and females, respectively).

(Life Science Research, Ltd., 1990)
TERATOLOGY STUDIES

1. Rat
Pyridaben was administered by gavage to groups of 22 pregnant CD rats at dose levels of 2.5, 5.7, 13 or 30 mg/kg/day from day 6 to day 15 of gestation inclusive. Groups receiving 13 or 30 mg/kg/day showed significant reductions in maternal weight gain during the treatment period. There was no effect at 2.5 and 5.7 mg/kg/day. Food consumption during the treatment period showed a dose-related reduction at 13 and 30 mg/kg/day, but was unaffected at lower dose levels. There was no effect on litter size or on pre- and post-implantation loss. Foetal and placental weights were reduced at 30 mg/kg/day and as a secondary effect a slightly retarded foetal development was seen at this level. A slight increase in the number of small foetuses was recorded and there were indications of visceral and skeletal immaturity, but no morphological changes were recorded that were considered to be related to treatment. There was no evidence of teratogenic effect in rats. The no-effect level was considered to be 5.7 mg/kg/day for maternal response, and 13 mg/kg/day for foetal response.

(Life Science Research, Ltd., 1988)

2. Rabbit
Pyridaben was administered by gavage to groups of at least 12 pregnant New Zealand White rabbits at dose levels of 1.5, 5 or 15 mg/kg/day from day 6 to day 19 of gestation inclusive. Pregnant rabbit receiving 15 mg/kg/day showed a transient, marked loss of bodyweight gain during the early part of the dosing period which was followed by a rapid, but partial recovery. This was accompanied by reduced food consumption and faecal output. Abortion was observed at the highest level. No consistent findings upon foetal development or survival in utero that were attributable to treatment were recorded. There was no evidence of teratogenicity in rabbits. The no-effect level was considered to be 1.5 mg/kg/day for maternal response and 15 mg/kg/day for foetal response.

Table 2 Mutagenicity studies.

<table>
<thead>
<tr>
<th>Method</th>
<th>Species, cell type</th>
<th>Test conditions</th>
<th>Results</th>
<th>Testing facility (Reporting year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ames test</td>
<td><em>Salmonella typhimurium</em> TA98, 100, 1535, 1537</td>
<td>Without S-9mix</td>
<td>Negative</td>
<td>Life Science Research, Ltd. (1986)</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em> WP2 worA</td>
<td>With S-9mix</td>
<td>Negative</td>
<td></td>
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<tr>
<td>Point mutation</td>
<td>Chinese hamster V79 cells</td>
<td>Without S-9mix</td>
<td>Negative</td>
<td>Life Science Research, Ltd. (1989)</td>
</tr>
<tr>
<td>in mammalian cell system</td>
<td></td>
<td>With S-9mix</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Chinese hamster lung (CHL) cells</td>
<td>Without S-9mix</td>
<td>Negative</td>
<td>Nissan Chemical Industries, Ltd. (1988)</td>
</tr>
<tr>
<td>in vitro</td>
<td></td>
<td>With S-9mix</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Micronucleus test</td>
<td>Male and female mice</td>
<td>Mortalities/clinical signs at the highest dose</td>
<td>Negative</td>
<td>Nissan Chemical Industries, Ltd. (1988)</td>
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<tr>
<td>in vivo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethal DNA damage in</td>
<td><em>Escherichia coli</em> WP2, WP67, CM871</td>
<td>Without S-9mix</td>
<td>No incidence of lethal DNA damage</td>
<td>Life Science Research, Ltd. (1986)</td>
</tr>
<tr>
<td>E. coli</td>
<td></td>
<td>With S-9mix</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>With S-9mix</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>
kg/day for foetal response.

(Life Science Research, Ltd., 1988)

MUTAGENICITY STUDIES

Pyridaben has been evaluated for mutagenic potential based on 3 endpoints as shown in Table 2. Pyridaben did not induce point mutations in bacterial or mammalian systems, tests for chromosomal aberration in vitro and micronucleus in vivo were negative, and pyridaben exhibited no effect on DNA damage in bacterial systems.

RAT METABOLISM STUDIES

Absorption, distribution, excretion and metabolism in rats were studied using pyridaben labeled with 2 separate 14C-labels, in either the pyridazinone or the benzyl ring. When a single dose of 3 mg/kg was orally administered to rats, elimination of pyridaben was rapid and almost complete within 96 hr. Absorption was between 38 and 46% of the dose administered and more than 80% of the absorbed pyridaben, labeled in either position, was excreted in the bile. The blood concentration was extremely low (maximum 0.04 ppm) and there were no significant residues in tissues. The pharmacokinetics of both a single oral dose of 30 mg/kg and repeated oral dose of 3 mg/kg was very similar to that of a single oral dose of 3 mg/kg in rats. Pyridaben was extensively metabolized to more than 30 metabolites, most of which were less than 3% of the dose. Pyridaben was metabolized by oxidation of the tert-butyl group and cleavage of the sulphur bond. A small amount of the cleavage moieties were conjugated with glucuronic acid or mercapturic acid.


PHARMACOLOGICAL STUDIES

The influence of pyridaben on body functions was examined in mice, rats, guinea pigs, rabbits and dogs. Since pyridaben is extremely insoluble in water, the test substance was suspended with 1% w/v sodium carboxymethyl cellulose and intragastrically administered in the case of experiments in vivo. In the in vitro experiments on isolated organs or blood etc., pyridaben was dissolved in 99.5% ethanol. Pyridaben had diarrhoea-producing effect at relatively low doses (3 to 10 mg/kg). Suppression of food consumption, hypothermia, bradycardia, decrease of urine excretion volume and bradypnoea were precipitated from the minimum acute toxic dose or near that dose (at 30 mg/kg or more for mice and 100 mg/kg or more for rats). At 300 mg/kg or more, greater effects were observed, and the central nervous and cardiovascular functions were markedly suppressed. However, no influence was observed on motor functions such as motor coordination, muscle strength or transmission at the neuromuscular junction even at doses causing severe toxic signs. No effects were observed on sensory and digestive organ function, on coagulation function in the blood at such dose levels, nor did it precipitate haemolysis. Pyridaben did not directly influence male or female reproductive organs. Emergency measures for the acute toxicity of pyridaben have been examined in rats, and gastric lavage in the early stage was found to be highly effective to prevent acute oral toxicity. Measures to treat diarrhoea which develops at relatively low doses of pyridaben have also been examined. In rats, loperamide produced marked antidiarrheal effects when administered prior to pyridaben and even when administered afterwards. No specific antidote for acute toxicity of pyridaben has been found to date.


FORMULATION TOXICITY STUDIES

1. Acute Studies

Acute studies were conducted on 20% WP and 20% SC formulations. The results are shown in Tables 3 and 4.

2. Primary Dermal Irritation Studies

The studies were conducted in accordance with Japanese MAFF guideline and the method of Draize. Neither formulation had any primary irritating potential on the skin of rabbits.

(The Institute of Environmental Toxicology, 1989)
3. Primary Eye Irritation Studies

The studies were conducted in accordance with Japanese MAFF guideline and the method of Draize. The WP formulation caused slight to mild irritation of the eye mucosa of rabbits. The SC formulation did not cause eye irritation in the rabbits.

(The Institute of Environmental Toxicology, 1989)

4. Dermal Sensitization Studies

4.1. Maximization test

The studies were conducted in accordance with the maximization method. Both formulations had moderate sensitizing potential in guinea pigs.

(The Institute of Environmental Toxicology, 1989)

4.2. Modified Buehler test

The studies were conducted in accordance with a modified version of the method of Buehler. Neither formulations elicited a delayed contact hypersensitivity in guinea pigs.

(Life Science Research, Ltd., 1990)

SUMMARY

The safety of pyridaben for users and consumers can be summarized as follows. The acute studies with technical material showed pyridaben to have moderate to low toxicity. Pyridaben caused no irritation of skin and eye and no contact sensitization. Pyridaben did not show mutagenic potential, was not oncogenic in rats and mice, did not affect reproductive performance in rats and was not teratogenic in rats and rabbits although decreases in bodyweight and food consumption were seen in teratology studies. In addition, the main effects seen in subchronic to chronic toxicity studies were the reduction of bodyweight gain, depression of food consumption and impairment of food conversion efficiency. A specific target organ, however, was not identified. The NOEL’s for chronic studies in rats, mice and dogs on a mg/kg bodyweight basis were comparable. The minimum value of the maximum no-effect level was 8 ppm in the oncogenicity study of mice. In conclusion,
there were no adverse toxicological findings based on the above studies.

Sanmite® WP and Sanmite® SC containing 20% pyridaben were registered by Japanese MAFF in 1991 as an acaricide and insecticide for various fruits as well as for tea. Pyridaben and its formulations were specified by Japanese MHW as harmful substances because of the acute toxicity data. However, the products are not considered to be a cause for concern in the safety of users and consumers provided they are used carefully and in accordance with the established standard for safe use.

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