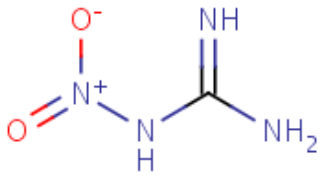
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

NITROGUANIDINE (NQ) (2016)

I. IDENTIFICATION

Chemical Name: 1-Nitroguanidine
Synonyms: Picrite; NQ; NG; Guanidine-1-nitro; Guanidine-nitro; NGu; N'-nitroguanidine; N(1)-nitroguanidine; α-Nitroguanidine; β-Nitroguanidine
CAS Number: 556-88-7
Molecular Formula: $CH_4N_4O_2$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1]

Physical State: Colorless crystalline solid. Long, thin, flat, flexible needles (alpha form); small, thin elongated plates (beta form).
Odor Description: Odorless
Molecular Weight: 104.07
Conversion Factors: None
Melting Point: 232 °C (decomposes)
Vapor Pressure: 1.43×10^{-11} mm Hg at 25 °C
Specific Gravity: 1.81
Density: 1.72 g/cm^3
Log K_{ow}: -0.89
Solubility: Slightly soluble in ethanol, alcohol; insoluble in ethyl ether; very soluble in alkali. Solubility in water 4.40 x 10^3mg/L at 25 °C
Stability: Stable
Reactivities and Incompatibilities: Reacts with oxidizing materials

III. USES[1,2]

Nitroguanidine (NQ) is typically used as a component of triple-base propellants. NQ has also been used commercially as a gas generator in automotive airbags, in anticorrosive phosphate coatings, and in the production of some pharmaceuticals.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Lethality Data

Species	Route	LD_{50} (mg/kg)
Rat	Oral	4,640 - 10,200; >5,000 [3–5]
Mouse	Oral	3,850 - > 5,000[4,5]
Guinea Pig	Dermal	3,120[5]

2. Eye Irritation

An *in vivo* eye irritation study following Good Laboratory Practice Standards, in New Zealand White rabbits demonstrated no eye irritation using the modified Draize scoring method and EPA test guidelines 560/6-82-001.[6]

3. Skin Absorption

In a Good Laboratory Practice Standards study conducted according to EPA guidelines 560/6-82-001, NQ applied dermally was not toxic in New Zealand White rabbits at doses up to 2 g/kg for 24 hours.[6] An additional study for which no details on methods were available demonstrated that NQ applied dermally in New Zealand White rabbits at doses up to 10 g/kg for 24 hours showed no toxic effects.[3]

4. Skin Irritation

In an *in vivo* NQ dermal irritation study in New Zealand White rabbits following EPA method 560/6-82-001 and Good Laboratory Practice Standards was found to be non-irritating using the modified Draize scoring method.[6]

5. Skin Sensitization

Guinea pigs were exposed to NQ following EPA test method 560/6-82-001 and Good Laboratory Practice Standards once a week for 3 weeks then challenged on week 5. The NQ response was scored according to Buehler's procedure. NQ did not cause dermal sensitization in this study.[6]

6. Acute Inhalation Toxicity

No data available.

B. Subacute Toxicity

1. Inhalation

No data available.

2. Oral Toxicity

Male and female Sprague-Dawley rats (10/sex/group) were administered NQ in feed at 0, 100, 316, or 1000 mg/kg/day for 14 days according to EPA test guidelines 560/6-82-001 and Good Laboratory Practices. No deaths occurred and no clinical signs associated with NQ administration were observed. Food consumption was not affected by NQ treatment; however, water consumption was increased in the 316 and 1000 mg/kg/day NQ groups for both males and females. Body weight changes observed first occurred during the quarantine period and were attributed to inadvertent water deprivation. This initial weight difference persisted throughout the study and, therefore, was not considered compound related. Organ weight and organ weight ratio effects were limited to reductions in heart weights in females in the 1000 mg/kg/day group. Microscopic examination of the control and high dose groups revealed no compound related lesions. Serum potassium levels were decreased in males in the 1000 mg/kg/day group. Serum calcium levels were reduced in males in all dose groups; however, this reduction was only significant in the 100 mg/kg/day group. The authors concluded that the increased water consumption and decreased electrolytes indicated that NQ may be acting as an osmotic diuretic.[7] A NOAEL of 316 mg/kg/day and a LOAEL of 1000 mg/kg/day were identified.

No significant effects were reported in a 30 day feeding study using male rats fed NQ at 0.01, 0.10, or 1.0% (equivalent to 9.3, 93, or 930 mg/kg/day).[3] No further details were reported.

C. Subchronic Toxicity

1. Inhalation

No data available.

2. Oral Toxicity

Male and female Sprague-Dawley rats (5/sex/group at interim sacrifice; 10/sex/group at terminal sacrifice) were given NQ via feed at 0, 100, 316, or 1000 mg/kg/day for 90 days according to EPA test guidelines 560/6-82-001 and Good Laboratory Practices. No mortality was observed during the study and no compound related clinical signs were observed. Food consumption in the 1000 mg/kg/day group was reduced compared to controls for both males and females, this reduction was significant during week 1 for males (7.7%), and weeks 5 (9.7%) and 6 (13.3%) for females. Reduced food consumption was attributed to poor palatability at higher concentrations. Water consumption increased in a dose dependent manner in both sexes, with the increase being statistically significant in the 316 and 1000 mg/kg/day groups. Male body weight was unaffected by NQ. Body weight of females in the 1000 mg/kg/day group was reduced (8-11%) compared to controls from week 5 through week 13, this decrease was statistically significant at weeks 5, 6, 8, 9 and 12. The reductions in body weight were attributed in part to reduced food consumption in the 1000 mg/kg/day group. Changes observed in organs weights were not dose dependent, were not statistically significant, and/or confounded by changes in body weight. No compound related abnormalities were observed upon microscopic examination of tissues in the control and 1000 mg/kg/day groups. Males in the 1000 mg/kg/day group had elevated cholesterol levels, while those in the 316 mg/kg/day group had reduced lactate dehydrogenase and total protein levels. Females in the 100 and 1000 mg/kg/day groups had elevated triglyceride levels. All clinical chemistry values were, however, within normal limits. Hematological values did not differ among treated and control groups. The NOAEL of 316 mg/kg/day and LOAEL of 1000 mg/kg/day were identified based on the deceased body weight in females and increased water consumption both sexes.[8]

Male and female ICR mice (5/sex/group at interim sacrifice; 10/sex/group at terminal sacrifice) were given NQ via feed at 0, 100, 316, or 1000 mg/kg/day for 90 days according to EPA test guidelines 560/6-82-001 and Good Laboratory Practices. No mortality was observed during the study and no compound related clinical signs were observed. Food consumption was not affected by NQ treatment; however, water consumption was increased in the 1000 mg/kg/day NQ groups for both males and females. No statistically significant changes in body weight or organ weights or weight ratios were observed at terminal sacrifice. At interim sacrifice, males in the 1000 mg/kg/day group had greater brain-to-body weight ratios than the controls, but absolute brain weights were not affected. No compound related abnormalities were observed upon microscopic examination of tissues in the control and 1000 mg/kg/day groups. Males in the 1000 mg/kg/day group had elevated aspartate amino-transferase (AST) levels at interim sacrifice (45 days), while those in the 316 mg/kg/day group had reduced uric acid levels. Females in the 316 and 1000 mg/kg/day groups had elevated albumin and albumin-globulin ratio values at interim sacrifice. All clinical chemistry values were, however, within

normal limits. Hematological values did not differ among treated and control groups. A NOAEL of 316 mg/kg/day and a LOAEL of 1000 mg/kg/day were identified based on the findings of increased water consumption in male and female mice.[9]

D. Chronic Toxicity/Carcinogenicity

No data available.

E. Reproductive/Developmental Toxicity

1. Developmental Toxicity

Sprague-Dawley dams (23-27 rats/group) were administered 0, 100, 316, or 1000 mg/kg/day NQ suspended in 1% carboxymethylcellulose via oral gavage. Dams were dosed on gestation days 6 through 15 based on day 6 body weight. Eight dams died or were euthanized during the study; five due to dosing errors (1 at 100- , 1 at 316-, and 3 at 1000-mg/kg/day) and three compound related (all 1000 mg/kg/day). Clinical signs of toxicity including red urine, hunched posture, dehydration, and red material on nose/forelimbs were observed in the 1000 mg/kg/day group during the treatment period. Dams in the 1000 mg/kg/day group lost weight during the treatment period and experienced significantly reduced weight (8-16%) compared to the control during the study period. Food consumption was significantly reduced in the 1000 mg/kg/day group during the treatment period. Fetuses were delivered by cesarean section on day 20. Gravid uteri and ovaries were examined; NQ had no effect on number of corpora lutea, implantations, resorptions, and live or dead fetuses. Fetuses were weighed, sexed, examined externally, and processed for visceral or skeletal examination. Male and female fetuses in the 1000 mg/kg/day group had decreased length and body weight compared to the controls. The number of fetuses, but not the number of litters, with skeletal variations (retarded ossification of the sternebrae, caudal vertebrae, and pubis) was increased in the 1000 mg/kg/day group compared to controls. Skeletal malformations occurred in two fetuses. One fetus in the 316 mg/kg/day group had anopthalmia, cleft palate, and small orbit with straight zygomatic arch. One fetus in the 1000 mg/kg/day group had a malformed orbit. Visceral malformations occurred in three fetuses; one control fetus had enlarged adrenals, one fetus from the 316 mg/kg/day group had abnormalities of the heart ventricles and hypoplasia of the lungs, and a fetus from a different litter in the 316 mg/kg/day group had a microphthalmia (small left eye) that was displaced medially. The malformations were considered spontaneous and not dose related because they occurred at a low frequency. The retarded development and skeletal variations observed in the high dose fetuses were attributed to maternal toxicity. There was no evidence of selective developmental toxicity of NQ in rats under conditions of this study. A NOAEL of 316 mg/kg/day and a LOAEL of 1000 mg/kg/day were reported for maternal and fetal toxicity. An free standing NOAEL of 1000 mg/kg/day was reported for developmental toxicity.[10]

In a pilot developmental toxicity study, Wistar rats (10/group) were dosed with NQ at 0, 10, 50, 100, or 500 mg/kg/day via oral gavage beginning on gestation day 6. The high dose group was terminated early (at days 16-17) due to a 50% mortality rate. The high dose group exhibited significant declines in body weight and food consumption. Clinical observations included ataxia, straub tail, impaired righting reflex, decreased motor activity, repetitive chewing, emprosthotonos, tip-toe walk, and hunched posture. Fetuses in the high dose group were either resorbed, dead, or viability could not be determined due to early gestational age. No treatment related effects were noted in lower dose groups. The reported findings were preliminary.[11]

New Zealand White rabbits (17-22 females/group) were administered 0, 100, 316, or 1000 mg/kg/day NQ suspended in 1% carboxymethylcellulose via oral gavage. Females were dosed on gestation days 6 through 18 based on day 6 body weight. Ten animals in the 1000 mg/kg/day group died or were euthanized during the study. Moribund animals exhibited signs of toxicity including convulsions, tremors, hypertonia, loss of consciousness, prostration, hunched posture, shallow rapid respiration, and dehydration during the treatment period. Clinical signs of toxicity were not observed in the 100 and 316 mg/kg/day groups. Thick foamy orange urine seen in treated animals was not an indicator of toxicity, it's merely an excretion of the test compound. Maternal body weight decreased in a dose-dependent manner during the treatment period; however, the reduction in weight was statistically significant only in the 1000 mg/kg/day group. Food consumption was reduced in the 1000 mg/kg/day group compared to the control during the dosing period. The authors attributed the reduced food consumption to the large quantity of material needed to achieve the 1000 mg/kg/day dose interfering with digestion. Food consumption returned to control levels in the post-dosing period and final body weight (corrected for gravid uterine weight) did not differ among treated and control groups. Fetuses were delivered by cesarean section on day 29. Gravid uteri and ovaries were examined; NQ had no effect on number of corpora lutea, implantations, and live or dead fetuses. Percent resorptions per litter (9.3, 6.6, and 17.9% (incorrectly reported by the authors as 9.7%), respectively) was significantly increased in the 100, 316, or 1000 mg/kg/day groups compared to the control (2.2%). The percent resorption in the concurrent

controls was considered by the study authors to be unusually low compared to historical control data. Historic data for the laboratory was not provided nor was the source for the referenced data. Published literature indicates resorption rates of 3.3 to 16% per litter for the species.[12] In the 100 mg/kg/day group, 12 out of 15 litters had only one resorption, two had no resorptions and only one doe had two resorptions. The typical incidence pattern for test article-related resorptions is clustered in a few does, not occurring at a low level among the entire dose group. In the 1000 mg/kg/day group, which was extremely toxic to the pregnant rabbits; one doe had eight resorptions, another doe had four resorptions and two does had two resorptions. This is a much different resorption pattern from the 100 mg/kg/day group and is the only dose level to display clear developmental toxicity. However, food deprivation or not eating due to toxicity is known to cause fetal loss (resorptions) and abortion in laboratory rabbits.[13–15] Fetuses were weighed, sexed, examined externally, and processed for visceral or skeletal examination. Male and female fetuses in the 1000 mg/kg/day group had decreased body weight (13.6 and 16.6%, respectively) compared to the controls. There were no differences in the rate of malformations among groups; only two fetuses, one at 100 and one at 1000 mg/kg/day groups, exhibited skeletal and/or visceral malformations. The number of fetuses with skeletal variations (reduced ossification of the sternebrae, olecranon, patellae, and phalanges) was increased in treated groups relative to the control group (38, 47, 47, 60% in the 0, 100, 316, 1000 mg/kg/day groups, respectively). The increase was only significant in the 1000 mg/kg/day group.[16]

The decrease in food consumption values and the mortality at 1000 mg/kg/day of NQ indicate that NQ was toxic to the does. The retarded development and skeletal variations observed in the high dose fetuses were attributed to maternal toxicity. Based on the patterns of toxicity observed, NQ has the potential to cause developmental toxicity (increased resorptions) in rabbits only at doses that are maternally toxic. A LOAEL of 1000 mg/kg/day and a NOAEL of 316 mg/kg/day were identified for maternal and fetal toxicity.[16]

2. Reproductive Toxicity

In a two-generation reproductive toxicity test, Sprague-Dawley rats (34-35 females and 24-25 males/group) were given NQ in the feed at 0, 1.3, 4.0, or 12.7 ppt, levels which, according to the authors would, in the young adult rats, approximate the 100, 316, and 1000 mg/kg/day doses used in previous developmental studies. Parental males and females were given treated feed for 10 weeks prior to mating, starting at 56 to 58 days of age, and continuously throughout mating, gestation, and lactation. The F1 and F2 generation animals received treated feed during weaning and thereafter. Parental males and females were paired for mating within the same dose group. Litters were examined and weighed on post-natal days 0, 4, 7, 14, and 21. Litter size was standardized to 8 pups on day four by random selection of an even number of males and females when possible. One male and one female from each litter were randomly selected to continue as parents for the next generation on post-natal day 21. The F1 animals were paired within groups for breeding at 18 weeks of age. NQ caused decreases in weekly body weights in the 12.7 ppt group F1 animals from the tenth week post-weaning until mating of the F1. Terminal body weights were lower for the 12.7 ppt group F1 males and females and 1.3 ppt group F1 females. Parental females in the 12.7 ppt group had decreased body weights compared to controls on gestation days 7, 14, 21 and lactation days 0 and 14. Body weight was reduced in the 12.7 ppt group F1 females on gestation days 14 and 21 and lactation days 0, 7, and 14. The 1.3 ppt group F1 females also had lower body weight compared to the controls on gestation day 21. NQ also had a slight effect on food consumption. Reduced food consumption occurred in the 12.7 ppt group for a few sporadic weeks during the study. There were no dose-related effects of NQ on clinical signs. Clinical signs, including red stains of the nose and hair loss on the limbs occurred in all dose groups. Irritability occurred at a higher rate in all of the F1 dose groups than the parental animals. There were no dose-related differences in the mating, female fertility, gestation, or live birth indices, length of gestation, number of live pups per litter, or sex ratio in either generation. The F1 offspring had lower viability and lactation indices in the 1.3 and 4.0 ppt groups; however, the viability and lactation indices did not differ from controls. The 1.3 ppt group had fewer pups surviving 4 days, while the 4.0 ppt dose had fewer pups surviving 21 days. The 12.7 ppt group had more missing and/or cannibalized pups during lactation days 8-14. Due to the absence of response in the high dose, the authors indicated that the decreased survival was not dose-related. In the F2 offspring, the 4.0 ppt group had more pups surviving 4 days than the controls. NQ did not affect pup weights or litter weights. Initial examination of pups and visceral examination on culled or dead pups demonstrated an extremely low incidence of findings which were varied and occurred in all dose groups. Dilated renal pelvis occurred more frequently in the F2 generation than the F1 and occurred in more pups (not litters) in the 12.7 ppt group than the control. Underdeveloped kidneys occurred more frequently in F2 than F1, but were not dose related. Histopathological examination of the reproductive organs on adult animals and gross examination of weanlings showed no lesions attributable to NQ in any of the generations. The authors

concluded that NQ did not cause reproductive or fertility toxicology effects in Sprague-Dawley rats under the conditions of the study.[17] A NOAEL of 4.0 ppt (316 mg/kg/day) and a LOAEL of 12.7 ppt (1000 mg/kg/day) were identified for systemic toxicity based on reduced body weight in parental females and F1 males and females.

A free-standing NOAEL of 12.7 ppt (1000 mg/kg/day) was identified for reproductive toxicity.

F. Genotoxicity/Mutagenicity

The genotoxicity of NQ has been evaluated using a variety of *in vitro* and *in vivo* test systems using guideline compliant protocols. The preponderance of negative findings demonstrates that NQ is not genotoxic.

1. In vitro

NQ was reported to be non-mutagenic in the Ames *Salmonella* test (TA98, TA100, TA1535, TA1537, and TA1538) conducted with and without activation with doses up to 5000 µg/plate.[18,19] NQ was evaluated using the revised Ames *Salmonella*/ mammalian microsome mutagenicity test (TA97, TA98, TA100, TA102, TA1535, TA1537, and TA1538), with and without metabolic activation (S9). NQ was not mutagenic using the pre-incubation modification and doses near the limit of solubility (2.8 mg/plate).[20]

The potential for NQ (0.01-3.9 mg/ml) to induce sister chromatid exchange (SCE) was evaluated in Chinese Hamster Ovary (CHO) cells. NQ did not induce a mutagenic response in the test system when tested up to doses near the limit of solubility of NQ in the pre-incubation mixture, with or without S9 activation.[21]

NQ tested at 1.25-5.0 mg/ml in the mouse lymphoma assay did not induce gene mutation in the TK+/- gene of mouse lymphoma cells (L5178Y). This assay, however, was conducted using un-induced mouse liver S9 preparation.[18] When tested in the presence and absence of an appropriately activated S9 system, NQ was similarly non-mutagenic in the mouse lymphoma thymidine kinase forward mutation assay at doses (1-4 mg/ml) that approached the solubility limits of NQ.[22]

NQ (10 mg/plate) was not active in the DNA repair assay using the *Escherichia coli* W3110/polA$^+$, p3478/polA$^-$ system.[19]

Mitotic recombinogenic tests of NQ (22.7 mg/mL) using cultures of the yeast *Saccharomyces cerevisiae D5* indicated no activity.[19]

NQ was tested for its ability to induce unscheduled DNA synthesis (UDS) in human embryonic lung cells (WI-38). Exposure to NQ (0.1-5 mg/ml) reportedly did not produce evidence for primary DNA damage in WI-38 cells directly or in the presence of uninduced mouse liver preparation (S9).[18]

2. In vivo

The mutagenic potential of NQ was evaluated in the *Drosophila melanogaster* sex-linked recessive lethal (SLRL) assay. The assay was conducted by mating males surviving 72 hours of feeding at approximately the LC_{50} (4-8 µg/ml) with untreated females. F1 females were then selected at random and mated with their sibling males. F2 progeny were examined for expression of the lethal mutation in treated males (*i.e.*, absence of round, red-eyed males). Negative (fructose) controls were similarly mated to untreated females. The frequency of mutations for the negative controls and NQ were 0.096% and 0.188%, respectively. NQ was determined to be non-mutagenic in the test system.[23,24]

The potential for NQ to induce dominant lethality was evaluated in mice and rats. Doses of 0.2, 0.67 and 2.0 g/kg were administered to males for five days. Males were mated with untreated females at weekly intervals for seven weeks. Females were euthanized two weeks after mating and uteri examined for dead/living fetuses, implantation sites and resorption sites. NQ did not cause a clastogenic response in the mouse germ cells. The study authors reported that NQ was also inactive in the rat dominant lethal assay; however, fertility indices were low in all control and test groups in the study, reducing sample sizes and inhibiting power to detect differences.[18]

G. Metabolism/Pharmacokinetics

Radiolabeled NQ [(^{14}C)NQ] was administered orally at 20 and 200 mg/kg and intravenously at 20 mg/kg to male and female rats. Blood samples were collected from 5 minutes to 24 hours post dosing, urine samples at approximately 4, 8, 24, 32, and 48 hours, and feces at 24 and 48 hours post dosing. Liver, heart, lung, kidney, spleen, brain, testes, ovaries, and muscle were collected 48 hours post treatment and analyzed for ^{14}C activity. Blood concentrations peaked within 1.5 hours. The volumes of distribution were 0.87, 0.85, and 0.66 l/kg for the 20 and 200 mg/kg oral and 20 mg/kg iv dose groups, respectively, and did not differ between groups. Absorption was not dose dependent and did not differ between males and females. The elimination half-life in whole blood was approximately 2 hours. One hour after oral dosing, NQ was found primarily in the gastrointestinal tract. NQ was evenly distributed throughout the body, with the exception of the brain where distribution was not significant.

After 48 hours, NQ was not found in any major organ. NQ was excreted unchanged in the urine; 40-50% within 4 hours, 62-81% with 8 hours, and 90-102% with 24 hours. NQ was not found in the expired air or feces.[25]

V. HUMAN USE AND EXPERIENCE

NQ has been used in munitions since World War I. In the U.S., the major use of NQ is as a component of triple-base propellant mixtures. NQ is also currently being investigated for use in insensitive munitions formulations. NQ has also been used commercially as a gas generator in automotive airbags, in anticorrosive phosphate coatings, and in the production of some pharmaceuticals.[2] NQ is manufactured at the Sunflower Army Ammunition Plant and is listed by the EPA as a High Production Volume (HPV) chemical.[12]

VI. RATIONALE

NQ did not induce skin irritation, eye irritation or skin sensitization responses in standard assays. Based on repeat-dose oral gavage studies in rodents, NQ induces acute clinical signs of toxicity, including lethality, beginning at doses of 500 mg/kg. The observed effects were non-specific and do not identify a specific systemic target for toxicity; effects were more severe in the gavage versus feeding studies. NQ has been evaluated for developmental toxicity studies in rats and rabbits. In addition, a multi-generation reproductive study in rats has been conducted.

Developmental effects observed in rats were all coincident with significant maternal toxicity, and generally occurred at high doses (1000 mg/kg/day). Based on observed effect levels, rabbits are more sensitive than rats to the developmental toxicity of NQ. In a standard developmental toxicity study in rabbits, increased fetal resorptions reported at 100 and 316 mg/kg/day did not follow the typical pattern of test-article induced resorptions. For this reason, it is not clear that the resorptions at the low doses were treatment related. Based on the evidence from the rat and rabbit developmental and reproductive toxicity studies, 316 mg/kg/day is the NOAEL and 1000 mg/kg/day is a LOAEL for both maternal and development effects. The point of departure for the WEEL derivation is 316 mg/kg/day.

Although there are well-conducted repeat-dose studies available for NQ, several key uncertainties in the overall data set exist. No toxicity data for NQ following exposure by the inhalation route were identified. Route-to-route extrapolation was used to derive the OEL and this approach is supported by the apparent lack of direct tissue reactivity of NQ and lack of irritant potential. No studies of the effects in humans were identified. A clear no effect level was not identified for the most sensitive adverse effect observed (fetal resorptions) and the dose-response for this endpoint did not support modeling to identify a surrogate no effect level. No chronic studies are available; however, based on the absence of clear systemic target organs effect, the lack of genotoxicity, and the toxicokinetic profile of NQ the absence of a chronic study is not a major data gap. A WEEL of 7 mg/m^3 as an 8-hour time-weighted average is recommended. No additional hazard notations are assigned.

VII. RECOMMENDED WEEL

8-hour Time-Weighted Average (TWA): 7 mg/m^3

VIII. REFERENCES

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