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OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: CHLORPYRIFOS - Registration of the Formulation XRM-5136 -
Acute Studies

Tox. Chemical No.: 219AA
Project Nos.: 9-1656 and 9-1657
MRID Nos: 411346-01, -02, -03, -04, -05 and -06
Record Nos.: 246798 and 246799

FROM: Alan C. Levy, Ph. D., Toxicologist *Alan C. Levy 12-19-89*
Review Section I, Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

TO: Dennis H. Edwards, Jr. PM # 12
Registration Division (H7505C)

THROUGH: Yiannakis M. Ioannou, Ph. D., Section Head
Review Section I, Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

J.M. Francis 12/19/89

and

Marcia van Gemert, Ph. D., Branch Chief
Toxicology Branch II (HFAS)
Health Effects Division (H7509C)

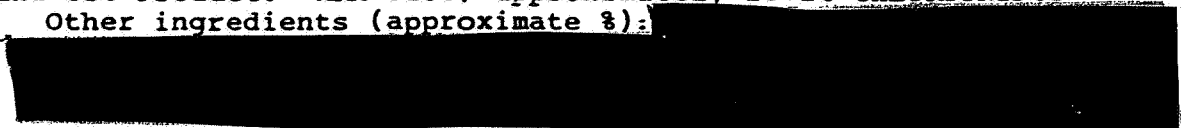
M van Gemert 12/21/89

Registrant: Dow Chemical Company
Midland, MI

Action Requested: Review acute toxicity studies in support of
registration of the end-use product (XRM-5136;
approximately 18.1% active ingredient CHLORPYRIFOS)

Chemical Information:

1. Active Ingredient: CHLORPYRIFOS [0,0-diethyl 0-(3,5,6-tri-chloro-2-pyridinyl) phosphorothioate]; 99% purity
2. End-Use Product: XRM-5136; approximately 18.1% CHLORPYRIFOS.
Other ingredients (approximate %):



10/11

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Studies Reviewed (Data Evaluation Reports attached):

1. Acute Oral Toxicity - Rat (§81-1) - MRID No. 411346-01

Animals: Fischer 344 rats; 5/sex/group
Doses (mg/kg): males = 100, 500, 1,000 and 2,000; females -
100, 500 and 1,000
Results: Mortality - 5/5 males at 2,000 dead by day 4
5/5 females at 1,000 dead by day 4
Clinical signs - tremors, lacrimation, salivation and
diarrhea
Acute Oral LD 50 - males = 1414 mg/kg; females = 707 mg/kg
Toxicity Category III
Classification: Core Guideline

2. Acute Dermal Toxicity - Rabbit (§81-2) - MRID No. 411346-02

Animals: New Zealand White rabbits; 5/sex
Dose (mg/kg): 2,000 mg/kg of undiluted XRM-5136
Results: all survived the 2,000 mg/kg limit dose (one male died
test day 4, not related to treatment)
Acute Dermal LD 50 (males and females) > 2,000 mg/kg
Toxicity Category III
Classification: Core Guideline

3. Acute Inhalation Toxicity - Rat (§81-3) - MRID No. 411346-03

Animals: Fischer 344 rats; 5/sex; plus 5 females at Time
Weighted Average (TWA)
Concentrations (mg/l, liquid aerosol): 3.73 for 4 hours to 5/
sex; 0.95 TWA to 5 females
Results: Mortality - by day 8, one male and 3 females at 3.73
mg/l
Clinical Signs - salivation, wet fur, lethargy, con-
gestion, incoordination, tremors, reduced body
weights and emaciation
LC 50 (mg/l): males > 3.73; females = about 3.12
Toxicity Category III
Classification: Core Guideline

4. Primary Eye Irritation - Rabbit (§81-4) - MRID No. 411346-04

Animals: New Zealand White rabbits; 5 male and one female
Dose: 18.2% XRM-5136, 0.1 ml into conjunctival sac
Results: slight redness of conjunctivae (6/6) post treatment;
all reversed in 72 hours post treatment
Conclusion: mild irritant
Toxicity Category III
Classification: Core Guideline

5. Primary Dermal Irritation - Rabbit (§81-5) - MRID No. 411346-05

Animals: New Zealand White rabbits; 4 males and 2 females
Dose: 0.5 ml of undiluted XRM-5136 (18.2% CHLORPYRIFOS) applied to intact skin for 4 hours
Results: within 30 minutes, 5/6 showed very slight erythema ("barely perceptible"); 1/6 well-defined erythema and very slight edema; all signs of dermal irritation gone 72 hours post treatment
Conclusion: very slightly irritating
Toxicity Category IV
Classification: Core Minimum

6. Acute Dermal Sensitization - Guinea Pig (§81-6) - MRID No. 411346-06

Animals: Hartley albino guinea pigs; 10 males
Treatment: Modified Buehler Method; 0.4 ml of undiluted XRM-5136; positive control group (10 additional animals) received 10% solution of DER 331 epoxy resin; exposure for 6 hours; procedure once/week for 3 consecutive weeks; challenge (undiluted XRM-5136 or DER 331) 2 weeks after last application
Results: no reaction to XRM-5136; positive control - slight to moderate erythema 8/10 animals
No appearance of delayed contact hypersensitivity.
Classification: Core Guideline

PRODUCT USE

XRM-5136 L.O. - Designed to control a large variety of pests in and around buildings and on various modes of transport.

Indoor use for crack, crevice, spot and broadcast treatments.
Outdoor use on surfaces of buildings and structures.

XRM-5136 TC - For use by commercial applicators for termite treatment. It is intended for treatment of soil, pre-construction subterranean areas, plenum structures, post construction areas, underground utility cable/conduit and utility poles/fenceposts.

CONCLUSIONS AND RECOMMENDATIONS

1. The data base for CHLORPYRIFOS is complete (no data gaps).
2. The submitted acute study data support the Registrant's label statements (40 CFR §162.10).
3. Toxicology has no objection to the registration of this product.

Reviewed by: Victor Miller Dip. Pharm. *V.M. 12/19/89*
Section I, Tox. Branch II (HFAS)
Secondary reviewer: Y.M. Ioannou Ph.D. *Y.M.I. 12/19/89*
Section I, Tox. Branch II (HFAS)

DATA EVALUATION REPORT

STUDY TYPE: Acute oral toxicity-rat (81-1)
MRID NO.: 411346-01
TEST MATERIAL: Chlorpyrifos
STUDY NUMBER(S): M-005136-001A
SPONSOR: The Dow Chemical Company, Midland, Michigan
TESTING FACILITY: Mammalian and Environmental Toxicology Research
Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland, MI 48674
TITLE OF REPORT: XRM 5136: Acute Oral Toxicity Study in Fischer
344 Rats
AUTHOR(S): M.J. Mizell, B.L. Yano and L.G. Lomax
REPORT ISSUED: May 17, 1989
CONCLUSIONS: Acute Oral LD50 = 1414 mg/kg (male rats)
Acute Oral LD50 = 707 mg/kg (female rats)
Toxicity category III
Classification of data: Core-guideline

METHODS:

Five (5) Fischer 344 rats of each sex, weighing 205 to 216 grams (males) and 132 to 134 grams (females), received doses of 100, 500, and 1000 mg/kg of the formulation, XRM-5136 by single-dose gavage. An additional group of five (5) males was given 2000 mg/kg. The chemical being tested was given as a 25% emulsion in water, the authors indicating that the formulation used in the study was prepared from samples of XRM-5136, which had been analyzed and found to contain 18.2% w/w chlorpyrifos. Animals were housed 2 to 3 per cage. Food and water were available ad libitum.

The animals were subsequently observed during a two week period for any signs of toxicity, including body weight changes, clinical manifestations and gross pathologic changes.

RESULTS:

All males and females given 100 or 500 mg/kg, and all males given 1000 mg/kg, showed no abnormal weight gain at study termination and were within normal limits at necropsy.

By the fourth day of the study, all males given 2000 mg/kg (5/5) and all females (5/5) given 1000 mg/kg had died. Clinical symptoms observed in animals that died and in survivors included tremors, lacrimation, salivation, diarrhea and perineal soiling from urine or diarrhea. These clinical signs are typical of organophosphate poisoning. Normal weight gains were observed in male and female rats given 100 or 500 mg/kg and all males given 1000 mg/kg.

No abnormalities were detected at necropsy.

CONCLUSIONS:

Acute Oral LD50 for male rats = 1414 mg/kg

Acute Oral LD50 for female rats = 707 mg/kg

Toxicity category III

Classification of Data: Core-guideline

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Reviewed by: Victor Miller Dip. Pharm.
Section I, Tox. Branch II (HFAS)
Secondary reviewer: Y.M. Ioannou Ph.D.
Section I, Tox. Branch II (HFAS)

V.M. 12/19/89
Y.M. 12/19/89

DATA EVALUATION REPORT

STUDY TYPE: Acute dermal toxicity-rabbit (81-2)
MRID NO.: 411346-02
TEST MATERIAL: Chlorpyrifos
STUDY NUMBER(S): M-005136-001D
SPONSOR: The Dow Chemical Company, Midland, Michigan
TESTING FACILITY: Mammalian and Environmental Toxicology Research
Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland, MI 48674
TITLE OF REPORT: XRM-5136: Acute Dermal Toxicity Study in New
Zealand White rabbits
AUTHORS: M.J. Mizell and L.G. Lomax
REPORT ISSUED: January 11, 1989
CONCLUSIONS: Acute dermal LD50 for male and female rabbits
>2000 mg/kg
Toxicity category III
Classification of data: core-guideline

METHODS:

Five New Zealand White rabbits per sex, weighing 2.2 to 2.6 kg, received a single dermal 24-hour exposure to 2000 mg/kg of undiluted XRM-5136 (Sample Reference: GHD 2380-24). The authors indicated that the formulation used in the study was prepared from samples of XRM-5136, which had been analyzed and found to contain 18.2% w/w chlorpyrifos. The animals were housed individually in animal care facilities. Food and water were available ad libitum.

The trunk of each rabbit was clipped free of fur 24 hours prior to application of test material, which was then applied to the back of each animal and held in contact with the skin by a gauze dressing and a non-irritating tape. A plastic wrap was placed around the trunk of the animal and secured. These wrappings were removed after a 24-hour period and observations were recorded for any irritation at the application site. The skin was washed, rinsed thoroughly and dried. The animals were fitted with a plastic collar to prevent ingestion of any residual material which may have remained after washing. The animals were subsequently observed during a two-week period for any signs of toxicity, including body weight changes, clinical manifestations and gross pathologic changes.

RESULTS:

All animals survived the 2000 mg/kg limit test established by the guidelines with the exception of one male rabbit submitted moribund to pathology on test day four for causes other than those related to treatment. Gross pathologic observations revealed that this rabbit had developed symptoms of mucoid enteropathy, a spontaneously occurring enteric disease of rabbits.

No gross pathologic changes were observed in any of the surviving animals, with normal weight changes being recorded during the course of the study. With the exception of the one rabbit referred to above, all other rabbits were within normal limits at necropsy.

CONCLUSIONS:

Acute Dermal LD50 >2000 mg/kg
for male and female rabbits

Toxicity Category III

Classification of Data: Core-guideline

007664

Primary Reviewer: Victor Miller Dip. Pharm.
Section I, Tox. Branch II (HFAS)
Secondary reviewer: Y.M. Ioannou Ph.D.
Section I, Tox. Branch II (HFAS)

V.M. 12/19/89
Y.M. 12/19/89

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity Study - Rats (81-3)

MRID NO: 411346-03

TEST MATERIAL: Chlorpyrifos

STUDY NUMBER(S): M-005136-003A
M-005136-003B

SPONSOR: The Dow Chemical Company, Midland, Michigan

TESTING FACILITY: Mammalian and Environmental Toxicology Research
Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland, MI 48674

TITLE OF REPORT: XRM-5136: An Acute Aerosol Inhalation Study in
Fischer 344 Rats

AUTHORS: M.J. Beekman, G.C. Jersey and J.E. Battjes

REPORT ISSUED: June 2, 1989

CONCLUSIONS: Acute Inhalation LC50 for male rats- >3.73
mg/liter
Acute Inhalation LC50 for female rats -
approximately 3.12 mg/liter

Toxicity category III

Classification of data: Core-guideline

METHODS:

Five rats per sex were exposed for four hours (whole body) to 3.73 mg/liter of a liquid aerosol of XRM-5136, a proposed termiticide (a formulation which has been analyzed and found to contain 18.2% w/w chlorpyrifos, reference no. GHD 2380-24, density of 1.067 g/ml). In addition a group of five female rats was exposed to a time-weighted average concentration of 0.95 mg/liter. The aerosol mass median aerodynamic diameter (MMAD) and geometric standard deviation were 2.45 μ and 2.21 μ , respectively. The average MMAD of the aerosol was 1.39 μ with a geometric standard deviation of 2.36 μ .

Nine and ten week old Fischer 344 rats (Charles River Breeding Laboratory, Kingston, NY) were individually housed in stainless steel wire cages during and following exposure. All animals were computer randomized and the rooms were regulated on a 12-hour photocycle. Food and water were supplied ad libitum.

Aerosols were generated by metering test material with a pump, mixing it with filtered compressed air and then spraying it into the chamber at a rate of approximately 30 liters per minute sufficient to provide normal concentration of oxygen to animals.

The animals were exposed for a single four-hour duration to a stable aerosol concentration, targeted to be the highest attainable. The second group of females was similarly exposed to a lower concentration. Gravimetric determinations were for the 3.73 and 0.95 mg/liter exposures were determined. Based on these determinations, the time-weighted average (TWA) exposure concentration was calculated. Prior to exposure all the animals were weighed and observed including a penlight ophthalmic examination by a laboratory veterinarian.

Animals were observed during the exposure period and daily during the two-week post-exposure period for evidence of toxicological and behavioral effects. On test days 2, 4, 8, 11 and 15 all rats were weighed. A complete gross pathological examination was conducted on each rat by a veterinary pathologist.

RESULTS:

By day 8, as a result of exposure to 3.73 mg/liter, one male and three female rats died. Transient effects observed initially included salivation, wet fur and redness around the nares. Lethargy, congestion and soiling of perineal region were also noted. All of the animals had encrustations around the muzzles, and some were mouth breathing. Further symptoms noted were incoordination, tremors and reduced body weights. Two female rats

appeared emaciated and one had tremors. At the end of the exposure period three males and one female rat appeared to have suffered no ill effects.

Animals exposed to 0.95 mg/liter had transient soiling around their muzzles and two of the five had slight soiling of the perineum with all returning to normal by the end of the exposure period. Mean body weights for males and females exposed to 3.73 mg/liter had decreased 19% and 18% respectively, by the end of the 14-day post-exposure period. However, body weights of females exposed to 0.95 mg/ liter surpassed pre-exposure values.

The outcome of a gross pathologic examination revealed that the one male and three female rats that had died during the initial phase of the study showed that exposure had resulted in changes consisting of wet haircoat, decreased ingesta, visceral congestion, stomach erosions and/or ulcers, perineal soiling, or hemolyzed blood, and/or gas in the digestive tract. Two/five males and one/five female that survived the post-exposure period had cloudy corneas, decreased body fat, facial soiling, thickened nonglandular mucosa of the stomach and/or erosions and/or ulcers of the glandular mucosa of the stomach. Thus two/five males and one/five female rat exposed to 3.73 mg/liter and all female rats exposed to 0.95 mg/liter were within normal limits.

It appears that administration of the test substance, XRM-5136 resulted in the above-mentioned signs and symptoms.

CONCLUSIONS: LC50 males = >3.73 mg/liter
LC50 females = approximately 3.12 mg/liter
Toxicity Category: III
Classification: Core-Guideline

007664

Primary Reviewer: Victor Miller Dip. Pharm. *V.M. 12/19/89*
Section I, Tox. Branch II (HFAS)
Secondary Reviewer: Y.M. Ioannou Ph.D. *Y.M.I. 12/19/89*
Section I, Tox. Branch II (HFAS)

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation Study- Rabbits (81-4)
MRID NUMBER: 411346-04
TEST MATERIAL: Chlorpyrifos
STUDY NUMBER(S): M-005136-001C
SPONSOR: The Dow Chemical Company, Midland, Michigan
TESTING FACILITY: Mammalian and Environmental Toxicology Research
Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland MI 48674
TITLE OF REPORT: XRM-5136: Primary Eye Irritation Study In New
Zealand White Rabbits
AUTHOR: M.J. Mizell
REPORT ISSUED: October 27, 1988
CONCLUSIONS: Chlorpyrifos appears to be a mild eye irritant.
Toxicity Category: III
Classification: Core-Guideline

METHODS:

The potential of XRM-5136, a formulation containing chlorpyrifos, to cause ocular irritation, was assessed. The authors indicated that the formulation used in the study XRM-5136, was prepared from samples that had been assessed and found to contain 18.2% w/w chlorpyrifos. This was done by instilling one-tenth (0.1) ml aliquots into the conjunctival sac of six New Zealand White rabbits (5 male and 1 female), weighing 2.8 to 3.2 kg. each. The left eye remained untreated and served as a control.

The animals were housed individually in animal care facilities. Food and water were available ad libitum. Twenty-four hours prior to the initiation of the study the eyes of the rabbits were examined with a 2% aqueous fluorescein stain and were found to be free of defects and irritation. The eyes of all the rabbits remained unwashed. Immediately after treatment, the rabbits were monitored for any irregular behavior symptoms, and both eyes were examined with a penlight at 1, 24, 48, and 72 hours post-instillation for conjunctival redness and chemosis, discharge, corneal opacity and reddening of the iris.

RESULTS:

All of the rabbits exhibited slight discomfort upon instillation of the test material, with subsequent examination of the conjunctivae post-treatment revealing slight redness in all animals. It was noted that four rabbits had reddening of the iris and the female rabbit had slight ocular discharge one hour post-instillation. All signs of ocular irritation were resolved within 72 hours post-treatment.

CONCLUSIONS: Chlorpyrifos appears to be a mild eye irritant.

Toxicity Category: III

Classification: Core-Guideline

Reviewed by: Victor Miller Dip. Pharm.
Section I, Tox. Branch II (HFAS)
Secondary Reviewer: Y.M. Ioannou Ph.D.
Section I, Tox. Branch II (HFAS)

N.M. 12/19/89 007564
J.M.L. 12/19/89

DATA EVALUATION REPORT

STUDY TYPE: Primary dermal irritation-rabbit (81-5)
MRID NO.: 411346-05
TEST MATERIAL: Chlorpyrifos
STUDY NUMBER: HET M005136-001B
SPONSOR: The Dow Chemical Company, Midland, Michigan
TESTING FACILITY: Mammalian and Environmental Toxicology Research
Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland, MI 48674
TITLE OF REPORT: XRM-5136: Primary dermal irritation study in
New Zealand White rabbits
AUTHOR: M.J. Mizell
REPORT ISSUED: October 27, 1988
CONCLUSIONS: The substance XRM-5136 is only very slightly
irritating to the skin of New Zealand White
rabbits.
Toxicity Category: IV
Classification: Core-Guideline

METHODS:

Aliquots of 0.5 ml of the undiluted formulation, XRM-5136, prepared from samples which had been analyzed and found to contain 18.2% w/w chlorpyrifos (DURSBAN XP), were applied for four hours to the intact skin of the back of six New Zealand White rabbits (four male and two female), weighing 2.7 to 3.3 kg. Animals were individually housed with food and water being available ad libitum.

Twenty-four hours prior to the test, 10cm² of the back of the six rabbits was clipped free of fur. The test substance was applied to the shaved area and covered with a gauze patch held in place with a non-irritating tape. The wrapping and gauze patch were removed after four hours and the back was wiped with a damp disposable towel to remove any residual test substance. The application sites were graded for erythema and edema within thirty minutes, 24, 48 and 72 hours. At this point the study was terminated.

RESULTS:

Within 30 minutes, five out of the six rabbits showed signs of very slight erythema ("barely perceptible") and one rabbit showed signs of slight well-defined erythema and very slight edema. All signs of dermal irritation were resolved 72 hours post-treatment.

CONCLUSIONS:

It appears that the substance XRM-5136 (chlorpyrifos) is only very slightly irritating to the skin of New Zealand White rabbits.

Toxicity category IV

Classification of data: Core-~~XXXXXX~~ *Guideline*

Primary Reviewer: Victor Miller Dip. Pharm. *V.M. 12/19/89*
Section I, Tox. Branch II (HFAS)
Secondary Reviewer: Y.M. Ioannou Ph.D. *Y.M.I. 12/19/89*
Section I, Tox. Branch II (HFAS)

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Sensitization Study (81-6)

MRID NUMBER: 411346-06

TEST MATERIAL: Chlorpyrifos

STUDY NUMBER: M-005136-001E

SPONSOR: The Dow Chemical Company, Midland, Michigan

TESTING FACILITY: Mammalian and Environmental Toxicological
Research Laboratory
Health and Environmental Sciences
The Dow Chemical Company
Midland, MI 48674

TITLE OF REPORT: XRM-5136: Dermal Sensitization Study in the
Hartley Albino Guinea Pig

AUTHORS: M.J. Mizell

REPORT ISSUED: October 31, 1989

CONCLUSIONS: XRM-5136 does not cause delayed contact
hypersensitivity in guinea pigs.

Classification of data: Core-Guideline

METHODS:

A liquid test formulation, XRM-5136, a proposed termiticide, containing 18.2% w/w chlorpyrifos (DURSBAN XP, Reference No. GHD 2380-24), was evaluated for dermal sensitization potential using a modified Buehler method.

Ten male Hartley albino guinea pigs (Charles River Breeding Laboratories, Inc., Kingston, NY), weighing 330 to 390 g, were used in this study. They were housed five per cage, being acclimated for at least one week prior to study initiation. Food and water were supplied ad libitum. Weights were recorded at initiation and termination of study. All animals were euthanatized at the end of the study.

Initially a preliminary skin irritation screen was carried out so as to determine a non-irritating concentration of the test material. A single application of 0.4 ml of 50% aqueous XRM-5136 or undiluted XRM-5136 was applied to the skin of one guinea pig for six hours. No dermal response was recorded at 24 and 48 hours post-exposure. Based on the results of this screen, the author of this study concluded that undiluted XRM-5136 was not irritating and was therefore chosen for this study.

Initially, during the induction phase of the study, the back of each guinea pig was clipped free of fur approximately 24 hours prior to study initiation. A four-tenths (0.4) ml aliquot of undiluted XRM-5136 was applied to the left side of ten guinea pigs in Hill Top Chambers, which were secured with non-irritating tape. A positive control group (an additional ten guinea pigs), received applications of a 10% solution of DER 331 epoxy resin in dipropylene glycol monomethyl ether in a similar manner. After a six-hour exposure period, the chambers were removed. The following day the animals were observed for any signs of erythema or edema. This procedure was repeated once a week for a total of three consecutive weeks.

The challenge phase of the study was carried out approximately two weeks after the last induction application. Having clipped the animals free of fur, undiluted XRM-5136 or 10% DER 331 was applied to the right side of the guinea pigs in the same manner as above. After six hours the chambers were removed and on the following day the application sites were depilated with Neet hair cream remover. All animals were observed and graded for sensitization response 24 and 48 hours after the challenge application. The authors of this study considered the test material to be a potential skin sensitizer if a positive response indicative of sensitization i.e. erythema and/or edema, was observed on two or more of the animals out of a total of ten animals tested.

RESULTS:

All animals remained in good health throughout and had gained weight by the end of the study. Challenge application of the positive control caused slight to moderate erythema in eight of the ten animals, six exhibiting a response after 24 hours and another two showing some mild degree of irritation 48 hours post-exposure. Challenge application of XRM-5136 caused no reaction in any of the animals.

CONCLUSIONS:

It appears that administration of the test substance, XRM-5136, did not cause delayed contact hypersensitivity in the guinea pigs tested.

Classification: Core-Guideline