MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 618-96, 618-97
AVID 0.15 EC, ZEPHYR 0.15 E C

FROM: William S. Woodrow WSW 12-11-91
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)
E 3/3/92

TO: G. LaRocca / Adam Heyward (PM 13)
Insecticide + Rodenticide Branch
Registration Division (H75-05C)

APPLICANT: Merck & Co., Inc Division of
Merck Sharp & Dohme Res. Labs.
Hillsborough Road
Three Bridges, N.J. 08887

FORMULATION FROM LABEL:

| Active Ingredient(s): | % by wt. |
|---|---|
| Avermectin $B_1$ [A mixture of avermectins containing 80% avermectin $B_{1a}$ (5-O-demethyl avermectin $A_{1a}$) and ≤20% avermectin $B_{1b}$ (5-O-demethyl-25-de(1-methyl propyl)-25-(1-methylethyl) avermectin $A_{1a}$)] | 1.9 |
| Inert Ingredient(s): . . . . . | 98.1 |
| Total | 100.0% |

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BACKGROUND

Merck & Co., Inc. submitted acute oral, two acute dermal toxicity, an acute inhalation, and a dermal sensitization study, to support registration of AVID 0.15 EC MITICIDE/INSECTICIDE (618-96), and ZEPHYR 0.15EC MITICIDE/INSECTICIDE (618-97).

The formulations for AVID 0.15 EC and ZEPHYR 0.15EC are identical, and acute toxicity data are submitted to support both products.

Previous reviews of acute toxicity data submitted to support Abamectin (Avermectin):

William Dykstra, Oct. 25, 1985

| Abamectin (Avid) | Tox. Category |
|---|---|
| acute oral $LD_{50} > 5.0$ g/kg | IV |
| acute dermal $LD_{50} > 2.0$ g/kg | III |
| acute inhalation $LC_{50} > 1.062$ mg/L | III |
| Eye irritation | III |
| Skin irritation | III |
| Der. Sen. guinea pig - negative | - |

William Dykstra: March 15, 1989

| | Tox. Cat. |
|---|---|
| acute oral > 5.0 g/kg | IV |
| acute dermal > 2.0 g/kg | III |
| acute inhalation $LC_{50}$ > 1.02 mg/L | III |
| Eye irritation - Corneal opacity absent by day 14 | II |
| Skin irritation, cleared by day 7 | III |
| Dermal sensitization - not a dermal sensitizer | - |

NOTE: Dykstra reviewed a new eye irritation study (3-15-89); MRID # 409125-01, Lab. # 11188-085-0, using "same formulation as Agrimek 0.15 EC."

Merck Sharp & Dohme changed the Avid 0.15 EC formulation to an alternative formulation which is the same as the Agri-Mek 0.15 EC formulation.

The formulation changes:

[redacted]

George LaRocca's letter to Merk (1-17-91) stated that the proposed change in formulation may alter the compound-related toxicity, and that therefore "a complete battery of acute toxicity data will be required". The request for new tox (acute) is based on Lucy Markarian's observation that [redacted] can enhance penetration through skin by the subject pesticide.

## RECOMMENDATION

1) The acute toxicity studies conducted with the alternate (new) product formulation (same as Agrimek 0.15 EC), that are acceptable, include: the acute oral, acute dermal, and the acute inhalation studies.

2) One of the acute dermal studies and the dermal sensitization study, were not acceptable, and were graded Supplementary:
   a. acute dermal MRID # 420203-02, Lab # TT-91-2607. - One dose test-results were < than 2 ml (2.0g/kg); LD50 not determined.
   b. dermal sensitization # 420203-04 (MRID) Lab. No TT # 91-638-0 - During epicutaneous

stage of test (maximization test), patches securing topically applied test mat. detached from skin, thus precluding valid test evaluation. (Tester stated compound ingredient probably dissolved adhesive material, however, 24 hour contact during acute dermal was successful. NOTE: When it became apparent that patches were insecure, double thickness aluminum foil should have been placed over patches and around trunks of animals.

3) Current acute toxicity profile for Awed 0.15 EC, Zephyr 0.15EC (EPA Reg. NOS. 618-96, and 618-97, respectively):

| Study | | MRID | Tox. Category | |
|---|---|---|---|---|
| acute oral | $LD_{50}$ = 304 mg/kg | 420203-01 | II | Guideline |
| acute dermal | $LD_{50}$ = 1.8 g/kg | 420798-01 | II | Guideline |
| acute inhalation | $LC_{50}$ = 3.5 mg/L | 420800-01 | III | Minimum |
| acute dermal | = < 2.0 g/kg | 420203-02 | - | Supplementary |
| dermal sensitization | not determined | 420203-04 | - | Supplementary |
| eye irritation - corneal opacity absent day 14 | | 409125-01 | II | Minimum |

(Dykstra 3-15-89) 4) The acute inhalation study (MRID NO. 420800-01), was graded Core Minimum Data: only mmad-GSD values presented; % particles by Impactor plates and % cumulative particles at and below each Impactor stage not presented.

5)

5) The following acceptable acute toxicity studies conducted using the current Avid 0.15 EC formulation must be submitted:

a. skin irritation study, and;

b. a dermal sensitization study

LABELING (both Avid 0.15 EC, and Zephyl 0.15 EC)

1) The WARNING signal word is appropriate.

2) Change the Precautionary Statements as follows:

"Causes substantial but temporary eye injury. May be fatal if swallowed or absorbed through skin. Do not get in eyes, on skin, or on clothing. Wear goggles, face shield, or safety glasses. Wear protective clothing and rubber gloves. Harmful if inhaled. Avoid breathing dust (vapor or spray mist). Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

3) Change the Statements of Practical Treatment as follows:

(Practical statements change)

"If Swallowed: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person.

If on Skin: Wash with plenty of soap and water. Get medical attention.

If in Eyes: Flush with plenty of water. Call a physician.

If Inhaled: Remove victim to fresh air. If not breathing, give artificial respiration, preferably mouth-to mouth. Get medical attention.

PM NOTE: Upon receipt of requested acute toxicity data, precautionary labeling may require revision.

PM NOTE: Both of the products presently being considered in this report (Zephyr 0.15EC Miticide/Insecticide [618-97] and Avid 0.15EC Miticide/Insecticide [618-96]) - contain identical formulations. Both products are intended to control mites and insects. Both products are

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supported by the same acute toxicity data. The product labels do indicate some differences in use/use patterns, however, one of these products is designated "restricted use only" 618-97, while the other product use is not restricted - 618-96. PM should consider whether or not both these products should be considered for restricted use.

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## DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

Product Manager: (13) 9-11-91
Reviewer: ~~M. Waller~~ Woodrow
MRID No.: 420203-01
Report Date: 12-4-91
Testing Facility: Merck Inst. for Therap. Res
Report No. TT#91-2606
Author(s): W. J. Bagden
Species: Rat, Crl:CD (SD)
Age: 6 to 7 weeks
Weight: 128-183g
Observation Days (Post Exposure): (14); other ( )
Source: Charles River Labs, Raleigh, L-676,863-3208-Spray formulation
Test Material: MK-0936 (Abamectin) - macrocyclic lactone dissaccharide.
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Conclusion: Density (Av.) = 0.96g/ml

1. $LD_{50}$ (mg/kg): Males = 0.319 ml/kg = 0.306g = 306 mg/kg Females = ~~.304 ml/kg = .292 mg = 292 mg/kg~~ Combined = 0.3166 ml = .304g = 304 mg/kg
2. The estimated $LD_{50}$ is
3. Tox. Category: II. Classification: Guideline

Procedure ~~(Deviations From §81-1)~~: ~~Groups~~ of 10M & 10F each were dosed by gastric intubation. Animals observed daily for mortality and clinical signs of toxicity for 14 days. Body wts recorded days 0 & 14.

Results:

Reported Mortality

| DOSAGE ( /kg) | (NUMBER KILLED/NUMBER TESTED) Males | Females | Combined |
|---|---|---|---|
| 0.25 ml/kg | 1/10 | 0/10 | 1/20 |
| 0.40 ml/kg | 10/10 | 10/10 | 20/20 |
| 0.64 ml/kg | 10/10 | 10/10 | 20/20 |
| 1.02 ml/kg | 10/10 | 10/10 | 20/20 |
| 1.63 ml/kg | 10/10 | 10/10 | 20/20 |
| 1.63 ml/kg (vehicle alone) | 0/10 | 0/10 | 0/20 |

Symptomology & Gross Necropsy Findings:

Clinical recovery b. wts: approx 20-25% less than control on dy 7; by day 14 recovery b. wts 10 to 15% < than controls. All rats dosed at 0.64, 1.02 & 1.63 ml/kg died beginning approx 2¼ to 22½ hrs post dosing. M rats dosed @ .4 ml/kg died 4 to 48 hrs & F about 7 hrs to 5th dy post dosing. All rats had tremors, ataxia, and/or bradypnea. Salivation, lacrimation

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more common at lower dose levels. Loss of righting usually preceded death. Some rats moribund from 3 hrs to 3 days prior to death.

Post Mortem:

Frequent upper dose gross observations included stomach distended, glandular mucosa brown, corroded, and some glandular mucosa green. Upper dose observations included lungs c red foci, red mottling. Lower dose(s) gross observations included liver c red or white foci, kidneys pale, c cysts, red mottling, enlarged pelvis.

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# DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: (13) 9-11-91 Reviewer: Woodrow ~~H. Waller~~
MRID No.: 420798-01 Report Date: 12-5-91
Testing Laboratory: ~~Merck Inst. for Ther. Res.~~ Report No. ~~TT~~#91-2628
Author(s): W.J. Bagdon
Species: Rabbit, NZ White
Sex: 15M+15F Wt.: 3.01 — 3.75 kg
Test Material: MK-0936 EC (L-676,863-320Y)
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)
Summary: assume density of 0.96 g/ml

1. $LD_{50}$ (mg/kg): Males = ~~—~~; Females = ~~—~~; Combined = ~~—~~;
2. The estimated $LD_{50}$ is > 1.8 g/kg
3. Tox. Category: II. Classification: Guideline

Procedure (~~Deviations From §81-2~~): Hair was removed from backs of 15M+15F rabbits ~ clippers: 10×10.4 cm area selected for study. 3 groups of 5M+5F separately with different dose of Test material. Dose applications to skin using syringe.
Results: Treated sites covered ~ 4×4" gauze, secured ~ tape.

Reported Mortality

| DOSAGE (g/kg) | (NUMBER KILLED/NUMBER TESTED) Males | Females | Combined |
|---|---|---|---|
| 1.0 g/kg | 0/5 | 0/5 | 0/10 |
| 1.4 g/kg | 1/5 | 0/5 | 1/10 |
| 1.8 g/kg | 1/5 | 0/5 | 1/10 |

~~Symptomology & Gross Necropsy Findings~~:
Treatment site then wrapped ~ clear polyethylene plastic collar on all animals during 24 hour exposure. Wrappings removed, sites wiped. Animals observed frequently day of Treatment (during 24hr exposure), & on days 3-9, 13, 14 & 15, animals removed from Cages & examined. Draize scoring used to evaluate dermal treatment sites.

Body weights recorded days 0, 7 & 15. All animals subjected to necropsy.

Results: 1 rabbit died at 1.8 g/kg, 1 died at 1.4 g/kg, and no mortality at 1.0 g/kg.

Clinical: Decreased food intake, decrease in stool amounts, ataxia, tremors, decreased activity, drooping lids - 3/10 @ 1.4 g/kg + 4/10 @ 1.8 g/kg - Scale formation seen in all surviving animals. Decrease in body weight of 5% at high dose, 2% at low and middle doses on day 8. All or most of weight regained by day 15.

Necropsy: Tester believes two male deaths due to inadvertent ingestion post-collar removal. Most rabbits exhibited skin scaling at application site. Remaining gross changes observed believed not to be treatment related.

12 DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: (13) 9-11-91 Reviewer: Woodrow ~~H. Walter~~
MRID No.: 420203-02 Report Date: 12-4-91
Testing Laboratory: Merck Inst. f. Therap. Res. Report No. TT#91-2607
Author(s): W. J. Bagdon
Species: Rabbit, NZ White, 36-37 wks old
Sex: 5M+5F (test), 3M+3F Vehicle: 3.13-3.78 kg
Test Material: MK-0936EC (L-676,863-320Y)
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)

Summary: Density = 0.96 g/ml Estimation of LD50 not possible.

1. $LD_{50}$ (mg/kg): Males = ——; Females = ——; Combined = ——
2. The estimated $LD_{50}$ is <2.1ml (2.0 g/kg) (2000 mg/kg)
3. Tox. Category: —. Classification: Supplemental

Procedure (~~Deviations From §81-2~~): Hair coat removed from back of 8M+8F rabbits, to expose an 10x10cm area. Test material (2.1ml) applied to clipped areas on backs of 5M+5F; 2.1ml vehicle alone applied to similar areas on backs of 3M+3F rabbits.

Results: Treated sites covered = 10x10 gauze patches secured = tape. Treated sites covered = clear plastic + secured.

Reported Mortality

| DOSAGE ( /kg) | (NUMBER KILLED/NUMBER TESTED) Males | Females | Combined |
|---|---|---|---|
| 2.1ml/kg (test) (MK-0936) | 4/5 | 2/5 | 6/10 |
| | | | |
| 2.1ml vehicle alone (control) | 0/3 | 0/3 | 0/6 |
| | | | |

~~Symptomology & Gross Necropsy Findings:~~

Plastic collars placed on each rabbit. Dressings removed after 24 hours - residual test material wiped off. Each rabbit examined for signs of toxicity and mortality - treatment sites examined daily according to Draize. Body wts recorded days 0, 7 + 14.

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Clinical: No systemic signs first 24 hours. Approx 1-4 hrs after patch removal, ataxia, broad-based tremors, lacrimation, drooping heads, loss of righting reflex and death (5 animals) seen in test group. 6 th rabbit dead on day 3. Surviving drug-treated rabbits appeared normal next day. No systemic effects noted in vehicle treated animals.

Necropsy: (Test animal(s)

Found dead: Epidermis application sites - patchy or diffuse brown/red discoloration, with or without scabbing. Overall grade ranged from moderate (4/6) to marked (2/6) skin damage.

Terminal necropsy: prominent scaling (at application site), crust formation, epidermal thickening, granulation. No other gross findings.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (13) 8-15-91 Reviewer: W. Woodrow
MRID No.: 420800-01 Report Date: 12-5-91
Testing Laboratory: Bio-Research Labs Senneville Quebec Report No. TT#91-9001
Author(s): R. Labbé
Species: Rat, Sprague Dawley
Sex: 96 in ♂95 ♀ Weight: 283-333g M, 175-227g F
Source: Charles River, Canada
Test Material: MK-0936 EC (Abamectin 0.15 EC, batch 005
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)
Summary: % by size ranges of particles not presented - cum. % part. at < each size range not u.

1. $LC_{50}$ (mg/kg): Males = 3.9 (3.5-4.3) mg/L ; Females = 3.1 (2.9-3.4) mg/L ; Combined = 3.5 (3.2-3.8) mg/L
2. The estimated $LC_{50}$ is
3. Mean Concentration:
4. Tox. Category : III . Classification: Minimum

Procedure ~~(Deviations From §81-2)~~: All animals acclimitized for 2 weeks prior to test. Groups of M + F rats exposed for 4 hours to test material doses, or to vehicle or air alone (controls). All animals examined 2 x

Results:

| Exposure Concentration (mg/L) | Reported Mortality (NUMBER KILLED/NUMBER TESTED) Males | Females | Combined |
|---|---|---|---|
| 2.77 mg/L (low dose) | 0/10 | 2/10 | 2/20 |
| 3.11 mg/L (low int. dose) | 0/10 | 8/10 | 8/20 |
| 3.41 mg/L (upper int. dose) | 5/10 | 8/10 | 13/20 |
| 4.06 mg/L (high dose) | 4/10 | 8/10 | 12/20 |
| air control | 0/10 | 0/10 | 0/20 |
| low vehicle control | 0/10 | 0/10 | 0/20 |
| high vehicle control | 1/10 | 0/10 | 1/20 |

~~Symptomology & Gross Necropsy Findings:~~ Daily for mortality and morbidity. Body weights were recorded on day 0, and on days 1, 2, 3, 6 and 13 and 14. Complete necropsies were performed on all animals. Exposures were nose only, volume

of 31 liters. Animals positioned in restraint cones. Exposure tube chamber contained port near breathing zone for air sample removal. Air flow through chamber 30 L/min., 20-24°C, 30-70% R.H. Test & control atmospheres generated using 2 single jet atomizers supplied with pressured air. Chamber conc. controlled by varying rate of aerosol delivery to chamber. The measured (wt. loss test mat. ÷ L air through chamber = mg/L) and the actual chamber concentration measured using gravimetric means. Increased filter weight(s) ÷ L air sampled = mg/L air. The particle size distribution was determined using an Anderson 1 ACFM Cascade Impactor. MMAD and GSD calculated.

Results: Chamber Concentration - Av. of 4 samples:

| | | | M | F | |
|---|---|---|---|---|---|
| Air control | 0.0000 | mg/L | 0/10 | 0/10 | 0/20 |
| low vehicle control | 2.7405 | mg/L | 0/10 | 0/10 | 0/20 |
| high " control | 3.8847 | mg/L | 1/10 | 9/10 | 1/20 |
| low dose | 2.7721 | mg/L | 0/10 | 2/10 | 2/20 |
| low intermed. dose | 3.1147 | mg/L | 0/10 | 8/10 | 8/20 |
| upper " dose | 3.4121 | mg/L | 5/10 | 8/10 | 13/20 |
| high dose | 4.0634 | mg/L | 4/10 | 8/10 | 12/20 |

Chamber concentration values (means of 4 samples), measured gravimetrically, as mentioned above.

Particle size analysis:

NOTE: The fraction (%) of particles collected by each Cascade Impactor stage, according to size ranges was not reported. Also, the cumulative % of particles, including and below each size range of the impactor (<), was not reported; only MMAD and G.S.D. values reported.

| Dose | MMAD | GSD |
|---|---|---|
| low vehicle control | 2.7μ | ± 2.2 |
| high " control | 2.3μ | ± 2.1 |
| low dose | 2.3μ | ± 2.1 |
| lower int. dose | 2.1μ | ± 2.1 |
| upper int. dose | 2.2μ | ± 2.2 |
| high dose | 2.0μ | ± 2.2 |

All treated and control animals showed body weight losses post exposure; weight losses were recovered and survivors body weights increased to the 14 day termination.

Clinical signs: tremors, cold body temperature, lacrimation, lack of balance, pallor, transient staining of muzzle or urogenital region.

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (13) 9-13-91 Reviewer: ~~M. Hahler~~ Woodrow
MRID No.: 420203-04 Report Date: 12-9-91
Testing Laboratory: Merck Sharp & Dohme Ltd. Report No. TT #91-638-0
Author(s): G. Durand-Cavagna
Species: guinea pig, Hartley
Sex: F Weight: 300-350g
Source: Charles River, France.
Test Material: MK-0936 EC 0.15%
Positive Control Material: dinitrochlorobenzene (DNCB)
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Method: Magnusson & Kligman (Modified)

Summary:
1. This product is / is not a dermal sensitizer. (not determined)
2. Classification: supplementary

Procedure ~~(Deviation From §81-6):~~ Testlab state that "the test procedure has been verified previously with dinitrochlorobenzene and other positive agents".

Solutions applied:

~~Results~~: ID (day 1) vehicle blank EC or MK-0936 0.15 EC were mixed with a volume of Freund's Complete Adjuvant. For epicutaneous applications (days 8 & 9), the vehicle blank EC or MK-0936 0.15 EC were applied undiluted. For epicutaneous applications on day 22 (challenge) the vehicle blank EC or MK-0936 0.15 EC were applied with an equal volume of dist. water.

Treatment groups:
Ten females control group.
11 females in vehicle blank EC group.
11 females in MK-0936 0.15 EC group.

A preliminary screen was conducted to determine

concentrations of test/vehicle materials to use in main test: 0.15ml MK-0936 0.15 EC or 0.15 ml of vehicle. Blank EC was irritating. 0.15 ml of MK-0936 0.15 EC diluted with an equal volume of dist. water was not irritating.

Induction:

ID Control group = Freund's Complete Adjuvant diluted with an equal vol. dist. water.

day 1) Vehicle blank EC Group - Vehicle diluted with an equal volume of Freund's Complete Adjuvant.

MK-0936 0.15 EC group - MK-0936 0.15 EC diluted with an equal volume of Freund's Complete Adjuvant.

Topical - on day 7 intra scapular area again clipped (day 8) and pre treated epicutaneously with approximately 400mg of 10% sodium lauryl sulfate in petrolatum - Days 8 & 9, 0.075ml of following placed over the intra dermal injection sites:

Control group: 2 x 0.075ml saline

Vehicle group: 2 x 0.075ml vehicle blank EC

MK-0936 0.15 EC group: 2 x 0.075 ml of MK-0936 0.15 EC.

NOTE: During concentration screen preliminary study, 0.3ml MK-0936 0.15 EC applied epicutaneously

for 48 hrs, covered ~ patches. However, patches were displaced, "probably due to dissolving properties of EC vehicle" - consequently both formulations were applied without patches on Days 8 & 9 (0.075ml) on each day - "this amount (0.05ml) is very small, and probably evaporated / and or became absorbed. On the other hand, the topical applications should have been covered with patches + aluminum foil for the full 48 hours in order for the test to be decisive.

Challenge: Day 22, two areas clipped on the right and left flanks of all animals.

Vehicle Blank 0.15ml of solutions.

Right flanks - saline + = pobdist MK207

Left flanks - vehicle, or MK-0936 0.15 EC (2x2 cm patches if moistened).

Control group

2x2 patches (whatman filter pap.) containing 0.15ml saline (right flanks), 2x2 cm patches containing either 0.15ml Vehicle blanks EC (left anterior flanks) or 0.15ml MK-0936 0.15 EC (left posterior flanks) diluted ~ equal vol. water. Patches secured with tape for 24 hrs & then removed.

Challenge sites read at 24 and 48 hours after patch removal. Scoring scale 0-3

| | | score |
|---|---|---|
| Control Group (not induced) | | |
| 24 hr & 48 hr | right anterior flank, saline | 0.00 |
| | left " " , vehicle Blank | 1/10 48 hr (1.0) |
| | left posterior " , MK-0936 0.15 EC, | 1/10 24 hrs, |
| | 2/10 @ 48 hrs. | |
| Vehicle Blank EC Group. (not induced) | | score |
| 24 & 48 hrs, | right flank saline | 0.00 |
| 24 hrs | Vehicle Blank EC & MK-0936 0.15 EC | 4/10 (1.0) |
| 48 hrs | " " " & " " | 4/10 (1.0) |
| MK-0936 0.15 EC Group (induced) | | |
| 24 & 48 hrs, | right flank saline | 0.00 |
| 24 hrs | , left " MK-0936 0.15 EC | 1/10 (2.0) |
| 48 hrs | , " " MK-0936 0.15 EC | 2/10 (1.2) |

Conclusion: It would appear that it is impossible to distinguish the control group(s) results from the animal results from induced animals (induced with test material) - lack of assurance that test material maintained in contact with test site for the prescribed 48 hours.