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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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FEB -5 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: GLUTARALDEHYDE. ID #043901-010352. Data Waiver Request for 21-Day Dermal Toxicity Study in Rabbit (Guideline 82-2) and Review of In Vivo and In Vitro Dermal Penetration Studies (Supplemental Data Submissions).

PC No.: 043901
Tox. Chem No.: 468
DP Barcode No.: D185596
Submission No.: S431023
DER Proj. No.: Intra-0311

FROM: Linnea J. Hansen, Ph.D.
Section IV, Tox. Branch I
Health Effects Division (H7509C)

TO: Linda DeLuise, Manager, PM Team 52
Kathryn Davis, Reviewer, PM Team 52
Accelerated Reregistration Branch
Special Review and Reregistration Division (H7508W)

THRU: Marion P. Copley, D.V.M., D.A.B.T., Section Head
Section IV, Tox. Branch I
Health Effects Division (H7509C)

Karl Baetcke, Ph.D., Branch Chief
Tox. Branch I
Health Effects Division (H7509C)
1/27/93

CONCLUSIONS:

DATA WAIVER REQUEST: TB-I will not grant a data waiver for the 21-day dermal toxicity study of glutaraldehyde in rabbits. This study was required in order to provide a more appropriate toxicity endpoint for risk assessment of short-term, repeated dermal exposure to glutaraldehyde than is presently available, and to better characterize systemic and dermal toxicity resulting from dermal exposure. The developmental toxicity study in rabbits, in which glutaraldehyde was administered by gavage, may not be appropriate for this purpose since human exposure to glutaraldehyde is primarily dermal and since toxicity is anticipated to be both quantitatively and qualitatively distinct by these two routes of administration due to glutaraldehyde's protein crosslinking/irritant properties. The other data cited by the Registrant ($LD_{50}$ and dermal penetration studies) do not

provide adequate information for risk assessment following dermal exposure. More detailed discussion follows below.

STUDY REVIEWS: Reviews of in vivo and in vitro dermal penetration studies previously submitted by the Registrant (MRID nos. 164185 and 418902-01, respectively) by Dr. Robert Zendzian are attached to this memorandum. The in vitro study was previously reviewed (HED Doc. #8879): this DER serves as an addendum to the original review. These studies were submitted voluntarily by the registrant and are not data requirements for reregistration of glutaraldehyde at this time.

In vivo dermal penetration in rats and rabbits (MRID #164185): Under the conditions of this study, $^{14}$C-glutaraldehyde at concentrations of 0.75% and 7.5% (approximately 6.2 and 60.7 mg/kg, respectively) was applied under occlusive wrap to shaved skin of male and female Fischer 344 rats or New Zealand White rabbits for 24 hrs. In rats, compound recovery ranged from 60 - 75% and dermal absorption ranged from 4.2% - 8.7%. In rabbits, compound recovery ranged from 72% - 100% and dermal absorption ranged from 41.9% - 45.5% (mean of 2 animals/dose/sex). However, dermal penetration was probably overestimated due to increased hydration of skin from use of occlusive wrap over treatment area. In IV studies, 0.075% and 0.75% glutaraldehyde were injected into male and female rats and rabbits for material balance studies 24 hr later. The primary route of elimination was via $CO_2$; at higher doses, this route appeared to become saturated. Radiolabel was also found in urine and feces, and highest tissue levels occurred in blood cells, spleen, lung and kidney.

Core-classification: Unacceptable (treatment area covered with occlusive wrap during absorption, thereby increasing permeability; dose per unit area not comparable in rat and rabbit, preventing species comparison). It should be noted that although this study is not considered acceptable, the dermal absorption values obtained may be used for a worst-case dermal absorption scenario.

In vitro dermal penetration of rat, rabbit, guinea pig, mouse and human skin (MRID #418902-01): Under the conditions of this study, $^{14}$C-glutaraldehyde at concentrations of 0.75% and 7.5% penetrated excised skin preparations from Fischer 344 rat, CD-I® mouse, New Zealand White rabbit, Hartley guinea pig or human female only slightly during a 6 hr exposure. Patterns of absorption by species, sex or dose were not always consistent. Dose absorbed/surface area ranged from 1.0 - 160 µg/cm and percent dose recoveries in media effluents ranged from 0.05% in female rat skin to 1.73% in male mouse skin at 0.75%. Dose absorbed/cm$^2$ was higher at the higher dose but dose applied/cm$^2$ was also higher and percent recovered was similar between the two doses. Rat and human female skin showed the least amount of dermal penetration; mouse and rabbit the highest. At 0.75%



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glutaraldehyde, male skin tended to absorb more compound than females, while females absorbed more than males at 7.5%.

Core-classification - Unacceptable (in vitro data not considered acceptable for dermal penetration because of difficulty extrapolating from in vitro to actual dermal absorption; dose per unit area different for each species).

**ACTION REQUESTED:**

In a letter from Joan E. Young dated December 10, 1992, Union Carbide Chemicals and Plastics Company, Inc. submitted a data waiver request for a 21-day dermal study in rabbits (Guideline 82-2). This request was sent in response to the Agency's recent Data Call-In.

In vivo and in vitro dermal penetration studies were previously submitted to the Agency for evaluation. These studies were submitted voluntarily by the Registrant as supplemental information on the dermal penetrability of glutaraldehyde and are not data requirements for reregistration of glutaraldehyde.

**DISCUSSION:**

Dr. Bryan Ballantyne, Director of Applied Toxicology at Union Carbide, responded to the Data Call-In for this study. Dr. Ballantyne believes that dermal toxicity of glutaraldehyde is probably both qualitatively and quantitatively different from oral (gavage) toxicity and that it is not "scientifically appropriate to extrapolate gavage data with an irritant chemical to the cutaneous route of exposure". TB-I agrees, and it is for that reason that a short-term, repeated dose dermal toxicity study is being required. The developmental toxicity study in rabbits, in which severe maternal toxicity and death at relatively low doses were observed, may not be an appropriate toxicity endpoint for short-term repeated exposure risk assessment when actual exposure to humans is primarily dermal. To the best of TB-I's knowledge, there are no carefully designed studies for determination of effects from short-term, repeated dermal exposure to glutaraldehyde. Estimation of risk to applicators may therefore be inaccurate and characterization of toxic effects inappropriate using a gavage study. TB-I agrees that dermal penetration of glutaraldehyde is not likely to approach 100%. Because of (1) the serious nature of the toxicity in the developmental study and (2) the possibility (as Dr. Ballantyne suggests) that toxicity resulting from gastrointestinal and dermal absorption of a protein cross-linking, irritating compound may be qualitatively and quantitatively distinct, TB-I considers a 21-day dermal study more appropriate for estimation of human risk and for determination of potential systemic and dermal toxic effects from dermal exposure.

Toxicity of glutaraldehyde is affected by concentration as well as total amount of compound (mg/kg body wt.) administered. Data on oral $LD_{50}$ values provided by the Registrant indicate that, at high concentrations (10 - 50%), the toxicity of glutaraldehyde administered orally is comparable on a volume/kg body wt. basis rather than on a mg/kg body wt. basis. Acute oral toxicity therefore is comparable even though mg glutaraldehyde/kg body wt. administered decreases ~5-fold. At high concentrations, toxicity of glutaraldehyde administered dermally (25 - 50%) is only slightly less than oral toxicity (2 - 5-fold). However, acute dermal toxicity of glutaraldehyde at concentrations below 25% is significantly less than acute oral toxicity (>10-fold). No data is available to compare dermal and oral toxicity following short-term repeated exposure at lower doses. The doses in the rabbit developmental toxicity study were administered at concentrations of less than 0.5%. It may therefore be expected that less toxicity is observed at comparable dermal doses.

At high concentrations glutaraldehyde is corrosive to skin. TB-I is aware that adjustments to the 21-day study protocol (eg: dose levels, duration of study) may be required if serious local dermal toxicity is observed at higher doses. The Agency should be notified of any proposed changes in study protocol. A preliminary study should help determine the appropriate study design.

Although the in vitro and in vivo dermal penetration studies previously submitted to the Agency (as additional toxicity information and not to fulfill data requirements) provide useful information, they are not considered acceptable (see attached reviews by Robert Zendzian). The in vitro study provided some information about relative penetration among species, but cannot be used to determine actual absorption. The in vivo study on rats and rabbits had experimental design problems which complicated interpretation of the results. Even if the dermal absorption data from this study were used to estimate human dermal absorption, the issue remains of using gavage data as the basis for estimation of dermal exposure risk of glutaraldehyde. MOEs for certain uses would also still be unacceptable. These studies together with the $LD_{50}$ studies therefore do not provide adequate information to estimate human risk from short-term repeated dermal exposure to glutaraldehyde.

Since glutaraldehyde is a widely used chemical with potentially significant toxicity, TB-I considers the 21-day dermal toxicity study an important part of the toxicity profile of glutaraldehyde. Union Carbide has no registered uses of glutaraldehyde as a wipe disinfectant, but use of Aqucar® 545 as a cooling tower biocide may pose a potential hazard to applicators when applied as a pour liquid (HED Doc. #9154).

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM September 14, 1992

SUBJECT: Glutaraldehyde, In Vivo and In Vitro Dermal Absorption Studies

TO: Linnea Hanson Ph.D.
Rev. Sec. IV, TB I
Health Effects Division (H7509C)

FROM: Robert P. Hendzian Ph.D. 10/14/92
Senior Pharmacologist
Health Effects Division (H7509C)

Action Requested

Review the following studies;

1) Skin penetration and pharmacokinetics of glutaraldehyde in rats and rabbits; J.A. McKelvey, C.M. Anuszkiewic and M.J. Tallant; Bushy Run Research Center; Project Report 47-197; Jan 15, 1985; MRID 164185

Core Classification IV acceptable
Dermal unacceptable

Conclusions

Intravenous and dermal plasma kinetics and material ballance studies of glutaraldehyde in water in rats and rabbits. Intravenous data technically sound, dermal data may over estimate penetration. Some evidence of an adverse effect on the dermal barrier. See DER for data and evaluation.

2) Glutaraldehyde: Species comparisons of In Vitro skin penetration following a single application to excised skin of humans, Fisher 344 rats, CD®-1 mice, Hartley guinea pigs and New Zealand white rabbits; M.J. Tallant, J.L. Beskitt and S.W. Frantz; Bushy Run Research Center; Project Report 53-157; Apr 2, 1991; MRID 418902-01

Core Classification Unacceptable

Conclusions

In vitro absorption through rat, mouse, guinea pig, rabbit

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and human skin from 0.75 or 7.5% solution. Results are internally inconsistant and inconsistant with our knowledge of relative species permeability. Some evidence of skin breakdown by the 7.5 % solution. Doses and dose presentation are not comparable with the in vivo rat study (MRID 164185) Data cannot be used for risk assesment purposes.

Discussion

The in vivo study reported provides some potentially very interesting data which, because of flaws in design of the dermal dosing portion, fails to reach its full potential. The study determines plasma kinetics and material ballance of $^{14}C$ glutaraldehyde following intravenous and dermal administration. The intravenous study is essentially flawless in design and the data look very good. The animals are dosed with a 0.07 or a 0.75% solution. The doses (on a mg/kg basis) are essentially the same for each species, sex and study type. This allows direct comparison of sex and species and the cross utilization of the results of the plasma kinetic data and the material ballance data.

In contrast the dermal study has flaws which cast doubt on the absolute values of dermal flux and make species comparison impossible.

The doubtfulness of the absolute values for dermal flux is due to the application site being occluded for the entire 24 hours of exposure. Thus the skin is hydrated and its barrier function is significantly decreased. This will visibly increase the penetration of a water soluble compound, by providing aqueous channels for penetration, so that the absolute values of flux can be expected to be much greater than would occur if the application site was exposed to air. Also, since the flux and the percent absorbed both increase with increasing concentrations of test compound, one can conclude that glutaraldehyde has a direct effect on the permeability of the skin. Dermal penetration is a saturatable process and under practical conditions the doses are either asymptotic to saturation or at saturation. Thus, the flux can increase with increasing dose (but not in a linear fashion) until saturation but the percent absorbed will concurrently decrease unless something affects the dermal barrier. Although the pattern seen here is more likely due to the test compound causing deterioration of the dermal barrier one cannot determine, or quantitate, if this is due to the test compound, dermal hydration or both.

The impossibility of comparing species follows from the differences in dose per unit area ((ug/cm$^2$) between rat and rabbit. For each solution concentration the dose per unit area is approximately four times greater in the rabbit than in the rat. As noted above, flux through the skin is dependent

on the dose to the skin in a nonlinear manner. Experience has shown than a change in unit area dose of more than two fold can be expected to change the relative flux in a manner which is not predictable without experimentally derived data.

The in vitro study was designed to compare in vivo and in vitro absorption in the rat and rabbit, the two species used in the in vivo study. It also included mouse, guinea pig and human skin to provide an internal in vitro comparision.

As the in vivo rat to rabbit comparison failed so did the in vivo-in vitro comparison fail because the doses used were not comparable on a mass per unit area basis. In vitro the skin samples were dosed with 0.75 and 7.5 percent glutaraldehyde in water solutions for doses of 1.06 and 10.6 $mg/cm^2$ respectively for all species and both sexes. The in vivo doses for rat and rabbit material ballance studies, which were designed to determine dermal absorption, were as follows;

| | Doses ($mg/cm^2$) | | | |
|---|---|---|---|---|
| Dosing Solution | Rat | | Rabbit | |
| | male | female | male | female |
| 0.75% | .031 | .030 | .131 | .131 |
| 7.5% | .300 | .304 | 1.308 | 1.234 |

In the process of dermal absorption, flux through the skin changes with dose to the skin, increasing with increased dose and decreasing with decreased dose. If the test compound has no effect on the barrier function of the skin, an increase of dose will ultimately saturate the process of dermal absportion and flux will become a constant. Thus, flux will not change with dose. At smaller doses the flux is asymtotic to saturation and will increase with increasing dose but the rate of increase in flux will decrease with increasing dose until the rate of increase in flux becomes zero. Because of the nonlinear relationship of dose and flux one must use the same dose when comparing the dose/flux relationship across species, sexes and in vivo versus in vitro.

Attachments
DERs
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Data Evaluation Report

Compound Glutaraldehyde

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Citation

Skin penetration and pharmacokinetics of glutaraldehyde in rats and rabbits; J.A. McKelvey, C.M. Anuszkiewic and M.J. Tallant; Bushy Run Research Center; Project Report 47-197; Jan 15, 1985; MRID 164185

Reviewed by Robert P Zendzian Ph.D. 9/10/92
Senior Pharmacologist

Core Classification IV acceptable
Dermal unacceptable

Conclusions

Intravenous and dermal plasma kinetics and material ballance studies of glutaraldehyde in water in rats and rabbits. Intravenous data technically sound, dermal data may over estimate penetration. Some evidence of an adverse effect on the dermal barrier. See DER for data and evaluation.

Materials

Glutaraldehyde-[1,5-$^{14}$C]
Lot # 1800-029
5.42% glutaraldehyde in water w/v
specific activity 3.03 mCi/mmole
radiochemical purity >99%
Lot # 1800-080
6.29% glutaraldehyde in water w/v
specific activity 3.98 mCi/mmole
radiochemical purity >99%

Glutaraldehyde
One quart 50%
Number IS-287201
analyzed 50.9% pure

Male and female Fisher 344 rats
60 days old
from Hilltop Lab Animals Inc.

Male and Female New Zealand White rabbits
4-5 months old
from Three Springs kennels

Experimental design

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Rats (four rats/group)

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Material ballance study

| Dose Solution | Males | | | Females | | |
|---|---|---|---|---|---|---|
| IV | mg | mg/kg | ug/cm$^2$ | mg | mg/kg | ug/cm$^2$ |
| 0.075% | 0.14 | 0.55 | - | 0.14 | 0.85 | - |
| 0.75% | 1.41 | 6.32 | - | 1.45 | 8.15 | - |
| Dermal | | | (49cm$^2$) | | | (48cm$^2$) |
| 0.075% | 0.16 | 0.69 | 3.3 | 0.16 | 0.91 | 3.3 |
| 0.75% | 1.54 | 6.33 | 31.4 | 1.44 | 9.40 | 30.0 |
| 7.5% | 14.7 | 62.7 | 300.0 | 14.6 | 103.6 | 304.2 |

Pharmacokinetic

| Dose | Males | | | Females | | |
|---|---|---|---|---|---|---|
| IV | mg | mg/kg | ug/cm$^2$ | mg | mg/kg | ug/cm$^2$ |
| 0.075% | 0.13 | 0.51 | - | 0.13 | 0.80 | - |
| 0.75% | 1.49 | 6.77 | - | 1.55 | 8.49 | - |
| Dermal | | | (49cm$^2$) | | | (48cm$^2$) |
| 0.75% | 1.50 | 6.49 | 30.6 | 1.40 | 8.58 | 29.5 |
| 7.5% | 14.6 | 62.9 | 297.8 | 14.9 | 100.2 | 309.8 |

Rabbits (two rabbits/group)

Material ballance study

| Dose | Males | | | Females | | |
|---|---|---|---|---|---|---|
| IV | mg | mg/kg | ug/cm$^2$ | mg | mg/kg | ug/cm$^2$ |
| 0.075% | 1.86 | 0.60 | - | 1.87 | 0.64 | - |
| 0.75% | 20.37 | 7.36 | - | 18.70 | 5.94 | - |
| Dermal | | | (144cm$^2$) | | | (144cm$^2$) |
| 0.75% | 18.92 | 6.36 | 131.37 | 19.00 | 6.18 | |
| 7.5% | 188.6 | 61.7 | 1308 | 177.7 | 58.6 | |

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Pharmacokinetic (plasma kinetics)

| Dose | Males | | | Females | | |
|---|---|---|---|---|---|---|
| IV | mg | mg/kg | ug/cm$^2$ | mg | mg/kg | ug/cm$^2$ |
| 0.075% | 1.87 | 0.63 | - | 1.89 | 0.63 | - |
| 0.75% | 18.77 | 6.40 | - | 18.63 | 6.05 | - |
| Dermal | | | (144cm$^2$) | | | (144cm$^2$) |
| 0.75% | 18.90 | 6.33 | 131.16 | 18.76 | 6.14 | 130.38 |
| 7.5% | 182.0 | 60.8 | 1264.5 | 179.5 | 60.6 | 1246.5 |

Animal preparation

Rats to be used for the pharmacokinetic studies had an indwelling venous cannula implanted in the right internal jugular vein on the day preceeding the experiment.

Animals to be dosed dermally had the hair clipped from the back on the day preceeding dosing. A 7 X 7 cm (male) or a 6 x 8 cm (female) area was marked on the back of each rat. A 12 x12 cm area was marked on the back of each rabbit.

Dose preparation and administration

"Dosing solutions were freshly prepared for each experiment. This was acomplished by mixing $^{14}$C-glutaraldehyde with nonlabeled glutaraldehyde in physiologic saline solution (0.9%) such that the appropriate concentration of glutaraldehyde and amount of radioactivity was contained in the targeted dose volume for each animal. The dosing volumes were held constant at 0.2 ml for rats and 2.5 ml for rabbits. Immediately prior to dosing, the pH of each common dosing solution was adjusted to pH 7.4 with 1N HCl or 1N NaOH as required."

Glutaraldehyde concentration of each dosing solution was determined.

For the IV studies the rat was anesthetized with Metofane® and 0.2 ml of the appropriate dosing solution was injected into the tail vein.

For the dermal studies in the rat, "the dose was administered under Metofane® anesthesia, using a tubercular syringe and 20 gauge needle, 0.2 ml of the appropriate dosing solution was applied to the skin area delineated by the marking pen. The dose was uniformly distributed over the entire dosing area with the aid of a glass rod. A piece of

polyethylene sheeting (approximately 10 x 20 cm) was then wrapped around the trunk of the rat and secured to the skin with Elastikon® tape. The occlusive dressing remained in place for the entire 24 houre experimental period.

In the rabbit IV study the dose was injected into the marginal ear vein.

In the dermal study "Rabbits were immobilized [on a restraining board] and the dose (2.5 ml) was applied to the skin area confined by the marking pen with a 3 ml syringe. In practice, approximately 0.5 ml of each dose was administered in 4-5 successive applications. After each application the dose was distributed uniformly over the dosing area with a glass rod. The dosing area was then occluded with a piece of polyethylene sheeting (approximatley 30 x 41 cm) as described in Appendix 2. The dosing area remained occluded for the entire 24-hour experimental period."

Sample collection

Pharmacokinetic studies

The IV dosed rats' blood samples were taken at 1, 3, 5, 10, 20, 30 and 45 minutes and 1, 2, 4, 6, 8, 10, 12, 16 and 24 hours. For the dermally dosed rats blood samples were taken at 10, 20, 30 and 45 minutes and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours.

Rabbits were immobilized for blood sampling. For the IV dosed animals blood samples were taken at 3, 5, 15, 30 and 45 minutes and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours. For the dermally dosed animals blood samples were taken at 15, 30 and 45 minutes and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours.

Material balance studies

Rats were housed individually in metabolism cages for the duration of exposure and urine and feces collected. Air was drawn through the cages and trapped to collect $CO_2$ samples for 5, 15 and 30 minutes and 1, 2, 4, 8, 12 and 24 hours. At termination the rats were sacrificed, the wrap collected from the dermally dosed animals and the exposed skin. Two skin samples were prepared for histologic and radioautographic examination and the remaining skin for $^{14}C$ activity. The following samples were collected from each rat (IV and dermal) and analyzed for radioactivity; plasma, blood cells, brain, lung, heart, thymus, liver kidneys, adrenal glands, spleen, pancreas, esophagous, stomach, small intestine, cecum, large intestine, GI contents, thyroid, salivary gland, trachea, bladder, ovaries or testes, lymph node, bone marrow, fat, muscle, skin (ear) and the remaining carcass.

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The same procedure was followed for the rabbits utilizing a specially designed metaboolism cage. Termination sample collection was the same as for the rats.

Results

Material ballance (as percent of administered dose) is presented in Tables 5 and 6 for rats and 7 and 8 for rabbits from the report. Mean absorption is presented below as the sum of urine, feces, cage washings, $CO_2$, tissues and carcass.

Mean Absorption
(percent of administered dose)

| Dose Concentration (%) | 0.075 | 0.75 | 7.5 |
|---|---|---|---|
| ug/cm$^2$ | 3.3 | 31.4 | 300.0 |
| Male rats | 4.75 | 4.21 | 6.42 |
| ug/cm$^2$ | 3.3 | 30.0 | 304.2 |
| Female rats | 5.61 | 6.89 | 8.72 |
| ug/cm$^2$ | ND | 131.37 | 1308.0 |
| Male rabbits | ND | 44.7 | 41.9 |
| ug/cm$^2$ | ND | 131.9 | 1234.1 |
| Female rabbits | ND | 45.5 | 41.9 |

ND not done

Tissue distribution of $^{14}$C-glutaraldehyde and/or metabolites is presented in tables 11 through 18 from the report.

Plasma concentration of radioactivity is presented graphically in figures 4 through 11 from the report.

Results of the microscopic examination of application site skin from the rats and the rabbits are presented in pages 1 through 5 from Appendix 6 of the report.

Discussion

The study reported provides some potentially very interesting data which, because of flaws in design of the dermal dosing protion, fails to reach its full potential. The study determines plasma kinetics and material ballance of

$^{14}C$ glutaraldehyde following intravenous and dermal administration. The intravenous study is essentially flawless in design and the data look very good. The animals are dosed with a 0.07 or a 0.75% solution. The doses (on a mg/kg basis) are essentially the same for each species, sex and study type. This allows direct comparison of sex and species and the cross utilization of the results of the plasma kinetic data and the material ballance data.

In contrast the dermal study has flaws which cast doubt on the absolute values of dermal flux and make species comparison impossible.

The doubtfulness of the absolute values for dermal flux is due to the application site being occluded for the entire 24 hours of exposure. Thus the skin is hydrated and its barrier function is significantly decreased. This will visibly increase the penetration of a water soluble compound, by providing aqueous channels for penetration, so that the absolute values of flux can be expected to be much greater than would occur if the application site was exposed to air. Also, since the flux and the percent absorbed both increase with increasing concentrations of test compound, one can conclude that glutaraldehyde has a direct effect on the permeability of the skin. Dermal penetration is a saturatable process and under practical conditions the doses are either asymptotic to saturation or at saturation. Thus, the flux can increase with increasing dose (but not in a linear fashion) until saturation but the percent absorbed will concurrently decrease unless something effects the dermal barrier. Although the pattern seen here is more likely due to the test compound causing deterioration of the dermal barrier one cannot determine, or quantitate, if this is due to the test compound, dermal hydration or both.

The impossibility of comparing species follows from the differences in dose per unit area ((ug/cm$^2$; between rat and rabbit. For each solution concentration the dose per unit area is approximately four times greater in the rabbit than in the rat. As noted above, flux through the skin is dependent on the dose to the skin in a nonlinear manner. Experience has shown than a change in unit area dose of more than two fold can be expected to change the relative flux in a manner which is not predictable without experimentally derived data.

GLUTARALDEHYDE

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Data Evaluation Report

Compound Glutaraldehyde

009996

Citation

Glutaraldehyde: Species comparisons of In Vitro skin penetration following a single application to excised skin of humans, Fisher 344 rats, CD®-1 mice, Hartley guinea pigs and New Zealand white rabbits; M.J. Tallant, J.L. Beskitt and S.W. Frantz; Bushy Run Research Center; Project Report 53-157; Apr 2, 1991; MRID 418902-01

9/10/92

Reviewed by Robert P Zendzian PhD
Senior Pharmacologist

Core Classification Unacceptable

Conclusions
In vitro absorption through rat, mouse, guinea pig, rabbit and human skin from 0.75 or 7.5% solution. Results are internally inconsistant and inconsistant with our knowledge of relative species permeability. Some evidence of skin breakdown by the 7.5 % solution. Doses and dose presentation are not comparable with the in vivo rat study (MRID 164185) Data cannot be used for risk assesment purposes.

Materials

Glutaraldehyde-[1,5-$^{14}$C]
Lot # 2534-069
1% glutaraldehyde in water w/v
specific activity 10.50 mCi/mmole
radiochemical purity 99%

Glutaraldehyde
2.5 gallons
Number IS-455-245
analysis not provided

Ethanol-1-$^{14}$C
Lot number 058F9218
specific activity 9.5 mCi/mmole
radiochemical purity >99%

Adult male and female Fisher 344 rats
10-12 weeks old
from Harlan Sprague Dawley

Adult male and female CD®-1 mice
5-7 weeks old
from Charles River

Male and female albino Hartley guinea pigs
5-7 weeks old
from Hazleton Dutchland Inc.

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Male and Female New Zealand White rabbits
Specific pathogen free
10-12 weeks old
from Hazleton Dutchland Inc.

Human skin samples
from women undergoing reconstructive mammoplasty
in the University of Pittsburgh Hospital system
ages 23-38 years

Experimental design

205 microliters of 0.75 or 7.5 % glutaraldehyde solution was utilized on in vitro skin preparations having a surface area of 1.77 $cm^2$ giving doses of 1.06 and 10.6 $mg/cm^2$ respectively. The experimental design and results are presented in Tables 1 and 2 from the report.

Experimental procedures

The experimental procedures are presented in Appendix I being sections Skin Preparation, Administration of Test Substance and Study Design: Skin Penetration and Material Ballance Determination from the report.

Results

Results are presented in Tables 1 and 2 from the report. Precent absorbed is summarized below in order from lowest to highest. No pattern either by species or dose is apparent. There is some indication of a compound induced deteriation of the dermal barrier by the higher concentration of glutaraldehyde.

| | | | | | |
|---|---|---|---|---|---|
| 0.75% solution (1.06 $mg/cm^2$) | | | | | |
| males | rat 0.6 | | guinea pig 0.53 | rabbit 0.77 | mouse 1.73 |
| females | rat 0.5 | human 0.16 | guinea pig 0.17 | mouse 0.26 | rabbit 0.34 |
| 7.5 % solution (10.6 $mg/cm^2$) | | | | | |
| males | rat 0.8 | | | mouse 0.39 | rabbit 0.85 |
| females | | human 0.20 | rat 0.33 | mouse 1.43 | rabbit 1.55 |

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GLUTARALDEHYDE

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