U.S. Department
of Transportation

**Research and
Special Programs
Administration**

400 Seventh Street, S.W.
Washington, D.C. 20590

OCT 1 1998

Mr. Richard M. Ormsbee
Minntech Corporation
14605 28th Avenue North
Minneapolis, MN 55447

Ref. No. 98-0232

Dear Mr. Ormsbee:

This is in response to your letter of August 12, 1998, requesting information on the determination of whether a material meets the definition for a Class 8 (corrosive) material under the Hazardous Materials Regulations (HMR; 49 CFR parts 171-180). Specifically you ask whether you may use the OECD guidelines (which require evaluation for 72 hours) to determine if a material is corrosive or if evaluation for 14 days is required to determine corrosivity for Packing Group II and III materials as provided by § 173.137. Your questions are paraphrased and answered as follows:

Q. Should the OECD guidelines be followed with the observation time extended to 14 days regardless of whether the material has shown full reversibility within a timespan of less than 14 days?

A. The OECD guidelines were adopted in the HMR to provide the method to determine whether a material meets the criteria for a Class 8 hazardous material. For purposes of classification under the HMR evaluation of up to 14 days is required for Class 8 materials in Packing Groups II and III as provided by § 173.137. However, if a material causes full thickness destruction of intact tissue in less than 14 days no further observation is necessary.

Q. When classifying a material as corrosive or non-corrosive is the OECD method acceptable with an endpoint observation of 72 hours?

A. The answer is no. For classification purposes of the HMR observation of up to 14 days is required.

I hope this satisfies your request.

Sincerely,

Thomas G. Allan

Thomas G. Allan
Senior Transportation Specialist
Office of Hazardous Materials Standards

LaValle
§173.136

MINNTECH

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98-0232

FAX COVER SHEET

DATE:	August 12, 1998	TIME:	9:52 AM
TO:	Edward T. Mazzullo	FAX:	202-366-3012
FROM:	Richard M. Ormsbee	PHONE:	612 551-2689
		FAX:	612-553-3387

RE: Observation times required for corrosivity testing

CC:

Number of pages including cover sheet: 1

Message

Mr. Mazzullo,

I would like to thank your office for the help that several people have provided me over the last couple of weeks. They have been very helpful in helping me understand several issues. I am writing you today to confirm that I properly understood the information that has been conveyed to me.

Once a material has been classified as a corrosive, a packing group must be determined using 49 CFR 173.137. In order to classify a material as Packing Group III, one must follow the 1992 OECD Number 404 protocol but extend the observation period beyond 72 hours as called out in the OECD protocol. The OECD Number 404 states "Further observations may be needed to establish reversibility", and the 49 CFR 173.137(c)(1) states "That cause full thickness destruction of intact skin within an observation period of up to 14 days ...". Am I correct to understand that the DOT wishes the OECD protocol to be followed, extending the observation times to 14 days regardless of whether a certain material has shown full reversibility within a timespan of less than 14 days?

My next question has to do with (1997) 49 CFR 173.136 Class 8 – Definitions. When classifying a material as corrosive or non-corrosive, the 1992 OECD Guideline for Testing of Chemicals, Number 404 is acceptable with an endpoint observation time of 72 hours?

Thank you for taking the time to answer and clarify these issues.

Sincerely,

Richard M. Ormsbee

Adopted:
17.07.92

OECD GUIDELINE FOR TESTING OF CHEMICALS

Adopted by the Council on 17th July 1992

Acute Dermal Irritation/Corrosion

INTRODUCTION

1. OECD Guidelines for Testing of Chemicals are periodically reviewed in light of scientific progress. In the review, special attention is given to possible improvements in relation to animal welfare. This updated version of the original guideline 404 (adopted in 1981) is the outcome of a meeting of OECD experts held in Paris in May 1991.

2. The main differences between this and the original version of the guideline are: a) the inclusion of data from *in vitro* tests in the information on which a decision not to proceed to an *in vivo* test can be based; and b) the possibility to use one animal in a first step of the *in vivo* procedure allowing certain chemicals to be exempted from further testing.

3. Definitions used are set out in the Annex.

INITIAL CONSIDERATIONS

4. In the interests of animal welfare, it is important that the unnecessary use of animals is avoided, and that any testing which is likely to produce severe responses in animals is minimised. Consequently, test materials meeting any of the following criteria should not be tested in animals for dermal irritation/corrosion:

i) materials that have predictable corrosive potential based on structure-activity relationships and/or physicochemical properties such as strong acidity or alkalinity, e.g., when the material to be applied has a pH of 2 or less or 11.5 or greater (alkaline or acidic reserve (1) should also be taken into account);

ii) materials which have been shown to be highly toxic by the dermal route;

iii) materials which, in an acute dermal toxicity test (2), have been shown not to produce irritation of the skin at the limit test dose level of 2000 mg/kg body weight.

In addition, it may not be necessary to test *in vivo* materials for which corrosive properties are predicted on the basis of results from *in vitro* tests (3).

PRINCIPLE OF THE *IN VIVO* TEST

5. The substance to be tested is applied in a single dose to the skin of one or more experimental animals, untreated skin areas of the test animal(s) serving as control. The degree of irritation is read

and scored at specified intervals and is further described in order to provide a complete evaluation of the effects. The duration of the study should be sufficient to evaluate fully the reversibility of the effects observed.. Animals showing severe distress and/or pain at any stage of the test must be humanely killed.

DESCRIPTION OF THE *IN VIVO* METHOD

Selection of animal species

6. Several mammalian species may be used. The albino rabbit is the preferred species.

Number and sex of animals

7. Three healthy adult animals are required for the complete test. Male and/or female animals can be used. Additional animals may be used to clarify equivocal responses. Sometimes the test can be performed with one animal only.

Housing and feeding conditions

8. Animals should be individually housed. The temperature of the experimental animal room should be 20°C (± 3°C) for rabbits, 22°C (± 3°C) for rodents and the relative humidity 30 to 70 per cent. Where the lighting is artificial, the sequence should be 12 hours light, 12 hours dark. Conventional laboratory diets are suitable for feeding and an unrestricted supply of drinking water should be available.

Preparation of the animals

9. Approximately 24 hours before the test, fur should be removed by close-clipping the dorsal area of the trunk of the animals. Care should be taken to avoid abrading the skin and only animals with healthy intact skin should be used.

10. Some strains of rabbit have dense patches of hair which are more prominent at certain times of the year. Such areas of dense hair growth should not be used as patch sites.

PROCEDURE

Application of the test substance

11. The test substance should be applied to a small area (approximately 6 cm^2) of skin and covered with a gauze patch, which is held in place with non-irritating tape. In the case of liquids or some pastes, it may be necessary to apply the test substance to the gauze patch and then apply that to the skin. The patch should be loosely held in contact with the skin by means of a suitable semi-occlusive dressing for the duration of the exposure period. Access by the animal to the patch and resultant ingestion/inhalation of the test substance should be prevented.

12. Liquid test substances are generally used undiluted. When testing solids (which may be pulverised if considered necessary), the test substance should be moistened with the smallest amount of water, or where necessary a suitable vehicle, needed to ensure good contact with the skin. When vehicles are used, the influence of the vehicle on irritation of the skin by the test substance should be taken into account.

13. At the end of the exposure period, normally 4 hours, residual test substance should be

removed, where practicable, using water or an appropriate solvent without altering the existing response or the integrity of the epidermis.

Dose level

14. A dose of 0.5 ml of liquid or 0.5 g of solid or semi-solid is applied to the test site.

Exposure of one animal

15. If it is suspected that the test substance might produce severe irritancy/corrosion, a single animal test should be employed. When it is suspected that the substance may cause corrosion, three test patches are applied simultaneously to the animal. The first patch is removed after three minutes. If no serious skin reaction is observed, the second patch is removed after one hour. If the observations at this stage indicate that exposure can humanely be allowed to extend to four hours, the third patch is removed after four hours and the responses are graded. If a corrosive effect is observed after either three minutes or one hour exposure, the test is immediately terminated by removal of the remaining patches. Alternatively, the three patches may be applied sequentially. When it is suspected that the substance may cause severe irritancy, a single patch should be applied to the animal for four hours.

Exposure of a further two animals

16. If neither a corrosive effect nor a severe irritant effect is observed after a four hour exposure, the test should be completed using two additional animals, each with one patch only, for an exposure period of four hours.

Exposure of three animals

17. If it is expected that the test substance will not produce severe irritancy or corrosion, the test may be started using three animals, each receiving one patch for an exposure period of four hours.

Observation period

18. The duration of the observation period should not be fixed rigidly but should be sufficient to evaluate fully the reversibility of the effects observed.

Clinical observations and grading of skin reactions

19. Animals should be examined for signs of erythema and oedema and the responses scored at 60 minutes, and then at 24, 48 and 72 hours after patch removal. Dermal irritation is scored and recorded according to the grades in the table below. Further observations may be needed to establish reversibility. In addition to the observation of irritation, all lesions and other toxic effects should be recorded and fully described.

TABLE: GRADING OF SKIN REACTION

Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4

Maximum possible: 4

Oedema Formation

No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 millimetre)	3
Severe oedema (raised more than 1 millimetre and extending beyond area of exposure)	4

Maximum possible: 4

Histopathological examination may be carried out to clarify doubtful reactions.

DATA AND REPORTING

Data

20. Data should be summarised in tabular form, showing for each individual animal the irritation scores for erythema and oedema at 60 minutes, 24, 48 and 72 hours after patch removal, all lesions, a description of the degree and nature of irritation, corrosion or reversibility, and any other toxic effects observed.

Test report

21. The test report must include the following information:

Test substance:

- physical nature and, where relevant, physicochemical properties;
- identification data.

Vehicle:

- justification for choice of vehicle.

Test animals:

- species/strain used;
- number, age and sex of animals;

- source, housing conditions, diet, etc.;
- individual weights of animals at the start and at the conclusion of the test.

Test conditions:

- technique of patch site preparation;
- details of patch materials used and patching technique;
- details of test substance preparation, application and removal.

Results:

- tabulation of irritation response data for each individual animal for each observation time period (e.g. 60 minutes, 24, 48 and 72 hours after patch removal);
- description of all lesions observed;
- narrative description of the degree and nature of irritation observed, and any histopathological findings;
- description of any other toxic effects in addition to dermal irritation/corrosion.

Discussion of the results.

If an *in vitro* test is performed before the *in vivo* test, the description or reference of the test, including details of the procedure, must be given together with results obtained with the test and reference substances.

LITERATURE

(1) Young J.R., How M.J., Walker A.P. and Worth W.M.H. (1988). Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances without testing on animals. Toxicology *In Vitro*, 2, 19-26.

(2) OECD, Paris (1987). Guideline 402.

(3) ECETOC Monograph No. 15, "Skin Irritation", European Chemical Industry, Ecology and Toxicology Centre, Brussels, July, 1990.

ANNEX

DEFINITIONS

Dermal irritation is the production of reversible inflammatory changes in the skin following the application of a test substance.

Dermal corrosion is the production of irreversible tissue damage in the skin following the application of a test substance.