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RECLASSIFICATION OF MATERIALS LISTED AS TRANSPORTATION HEALTH HAZARDS --- SUPPLEMENT I

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FINAL REPORT

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16. Abstract This final report on a contract between the Department of Transportation and the United States Air Force Toxic Hazards Laboratory supplements the acute toxicity data reported in TSA-20-72-3. In the previous report the toxicity of several compounds of interest to the Department of Transportation was discussed. This was done in the light of a reexamination of existing data or the determination of acute toxicity data on those compounds where no previous data existed. The information so gathered was used to help reclassify these compounds into categories which may help to define shipping and handling requirements concomitant with the hazard associated with each compound. The classifications assigned are not official regulatory classifications and are presented for technical information only. Seven new compounds were examined in this same light to provide additional information to the Department of Transportation. These compounds are as follows: mixed cresols, allyl isothiocyanate, methyl isothiocyanate, methyl isocyanate, ortho-nitroaniline, ethyl chloroacetate and phenyl isocyanate.					
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Reclassification of Materials Listed as

Transportation Health Hazards --- Supplement I

This final report on a contract between the Department of Transportation and the United States Air Force Toxic Hazards Laboratory supplements the acute toxicity data reported in TSA-20-72-3. In the previous report the toxicity of several compounds of interest to the Department of Transportation was discussed. This was done in the light of a reexamination of existing data or the determination of acute toxicity data on those compounds where no previous data existed. The information so gathered was used to help reclassify these compounds into categories which may help to define shipping and handling requirements concomitant with the hazard associated with each compound. The classifications assigned are not official regulatory classifications and are presented for technical information only.

Seven new compounds were examined in this same light to provide additional information to the Department of Transportation. These compounds are listed below:

1. mixed cresols
2. allyl isothiocyanate
3. methyl isothiocyanate
4. methyl isocyanate
5. ortho-nitroaniline
6. ethyl chloroacetate
7. phenyl isocyanate

The materials were classified as requested by the Department of Transportation according the "Extremely Toxic" and "Highly Toxic" criteria shown in the Second Advance Notice of Proposed Rule Making Docket No. HM-51 (36 F. R. 2934), published February 12, 1971.

A third classification of "Toxic" was used for some of the materials which did not fall in the above "Extremely Toxic" or "Highly Toxic" categories, but for which adequate data was available for classification. We were concerned that the uses of the proposed revised commodity list would misinterpret the lack of classification as meaning nontoxic.

Most of these materials are toxic and, therefore, we have classified them as such for consideration by the Department of Transportation.

The "Toxic" classification is a direct downward classification of the acute LD₅₀ and LC₅₀ levels used in the "Extremely Toxic" and "Highly Toxic" levels, mentioned previously. It corresponds to the "Toxic Substances" category found in Section 191.1, Title 21 - Food and Drug, CFR, Revised as of January 1, 1970. The classification system used is shown below:

	<u>Extremely Toxic</u>	<u>Highly Toxic</u>	<u>Toxic</u>
Inhalation, 1 Hour LC ₅₀	500 mg/m ³ or less (50 ppm or less)	>500-2000 mg/m ³ (>50-200 ppm)	>2000-200,000 mg/m ³ (>200-20,000 ppm)
Oral, 14-Day Single Dose LC ₅₀	5 mg/Kg or less	>5-50 mg/Kg	>50-5000 mg/Kg
Skin Absorption (Dermal) LD ₅₀	20 mg/Kg or less	>20-200 mg/Kg	>200-20,000 mg/Kg

Since the new classifications were based solely on acute toxicity, all forms of a material (concentrates, solutions, mixtures, etc.) have been assigned to the same toxicity categories regardless of concentration of the active ingredients. No consideration was given to hazard potential of the materials reclassified. For purposes of uniformity all inhalation toxicity data was converted to mg/m³ if given in other units of measurement. These values may be converted to parts per million by use of the following formula:

$$\text{ppm} = \frac{24.50 \times \text{mg/m}^3}{\text{mol. wt.}}$$

Conversion of units from mg/m³ to ppm may, in certain instances change the classification in which borderline compounds may fall. In those instances where this happens the mg/m³ unit should take precedence.

All seven compounds listed previously were administered to rabbits to determine skin absorption LD₅₀ values, and three of the seven compounds (allyl isothiocyanate, methyl isothiocyanate and methyl isocyanate) were administered orally to both rats and mice to determine the LD₅₀'s in each of these species. These studies were designed to define the acute toxic response of the subject compound resulting from single accidental exposure and do not define the potential total hazard of carcinogenic risk or inhibition of performance of emergency duties including self rescue.

For the determination of oral toxicity, the following methods were used:

Male CFE rats (200-300 grams) and male CF-1 mice (20-30 grams) were used in this study.

The compounds were given as a suspension in corn oil and the suspensions were kept in a turbulent state while in use. Glass syringes with special oral dosing needles were used to administer the compounds to the rodents. The experimental animals were fasted overnight prior to administration of the oral dose. This allowed for more uniform absorption, since the amount of food in the stomach varies greatly from animal to animal in the unfasted condition. The injected volumes of test compounds for the rodents were approximately 0.01 ml/gm. This resulted in the average mouse receiving a volume of 0.25 ml, and the average rat a volume of 2.5 ml. Both mice and rats were weighed individually at the time of dosing to determine the proper dose volume.

Range-finding doses were given for each compound. These consisted of intubating five rats and five mice each at three dose levels estimated from available evidence in the literature, or if information was not available, dose levels of 5 mg/kg, 50 mg/kg and 500 mg/kg were used. Results of the range-finding tests served to determine whether doses needed to be higher or lower. After finding the proper range, geometrically spaced doses were administered to determine the actual LD₅₀. Five rats and five mice were dosed at each level, and the LD₅₀ with its 95% confidence limits was calculated using the moving average interpolation method.

Deaths which occurred during the 14 days immediately following the administration of the single dose were included in the final mortality tally.

For the dermal absorption toxicity determinations, female albino New Zealand rabbits weighing approximately 5 pounds were used as the experimental animals. All rabbits were clipped as closely as possible with an Oster clipper having surgical blades and a vacuum attachment. The back of the rabbits and the sides down to about half way to the stomach area were clipped from the saddle area of the shoulders to the top of the rear leg area.

The animals were individually weighed to determine the proper dose volume. The measured volume of the liquid material was then applied undiluted to the back of the rabbit and was divided as equally as possible between the two sides of the back. If the volume was sufficiently great, the dose was kept in place by applying 8-ply gauze patches over the liquid on each side of the back. A patch of latex rubber dental dam or vinyl plastic, whichever was most compatible with the compound being tested, was then applied over the entire back area where clipped, and elastoplast tape was used to wrap the entire midsection of the rabbit to keep the gauze in place. Specially designed rabbit restraining

harnesses were fitted to each rabbit at the time of treatment. These harnesses restricted undesirable movement of the rabbits, i. e. , prevented them from chewing on the taped area. The harnesses did, however, allow the rabbits complete freedom to eat and drink during the 24-hour restraining period.

All compounds were applied undiluted. The single solid material (ortho-nitroaniline) was applied in coarse powder form held in place with gauze patches and a rubber dental dam.

The test compounds remained in contact with the rabbit's skin for 24 hours. After this period of time, the gauze tape and harness were removed. The rabbits were observed for signs of toxicity or death during the 14 days immediately following dosing. The classification of these compounds is shown in Table I. Data sheets listing LD₅₀ values and justification for each classification are attached in Appendix A. Information concerning the source, lot number and purity or grade of the individual compounds is given in Appendix B.

Although classification of irritation effects of those compounds was not a part of this study, the very potent lacrimation induction by several of the compounds, most notably the isocyanates, was impossible to overlook. These properties would certainly have to be considered when establishing safety regulations for the handling and storage of these compounds.

TABLE I. CLASSIFICATION OF COMPOUNDS BASED ON ACUTE TOXICITY TESTS

<u>Code Number</u>	<u>Name</u>	<u>Toxicity Classification</u>
103	ortho-nitroaniline	Toxic
246	cresols, mixed	Toxic
249	allyl isothiocyanate	Highly Toxic
250	ethyl chloroacetate	Toxic
251	methyl isothiocyanate	Highly Toxic
252	methyl isocyanate	Toxic
253	phenyl isocyanate	Toxic

APPENDIX A

DATA SHEETS

TOXICITY DATA SHEET

COMPOUND: ORTHO-NITROANILINE

CODE: 103†

CLASSIFICATION: TOXIC

INHALATION TOXICITY

SPECIES	CONC. *	SYS. **	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Other	_____	_____	_____

ORAL TOXICITY

SPECIES	DOSE***	SYS. **	REF.
Man	_____	_____	_____
Rat	3564	LD ₅₀	_____
Mouse	1288	LD ₅₀	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Cat	_____	_____	_____
Guinea Pig	_____	_____	_____
Other	_____	_____	_____

OTHER ROUTES OF ADMINISTRATION

	SPECIES	ROUTE	DOSE***	SYS. **	REF.
1.	Rabbit	Dermal	20,000	Nonlethal	
2.					
3.					
4.					
5.					
6.					

* Concentration in mg/M³
 ** System for expression of toxicity
 *** Dose in mg/Kg
 † Revised 1973

JUSTIFICATION:

Data generated under contract between the Department of Transportation and
United States Air Force Toxic Hazards Laboratory.

Rat 14-Day Oral LD₅₀ = 3564 mg/kg
95% Confidence Limits (2590-4910)

Mouse 14-Day Oral LD₅₀ = 1288 mg/kg
95% Confidence Limits (1131-1467)

Rabbit 14-Day tests after 24 hours skin contact of 20,000 mg/kg
were nonfatal indicating poor absorption of ortho-nitroaniline
through the skin. Exposure levels above the value are meaningless.

The oral toxicity data fall in the "Toxic" category.

REF.

TOXICITY DATA SHEET

COMPOUND: CRESOLS (Mixed ortho, meta and para forms) CODE: 246†

CLASSIFICATION: TOXIC

INHALATION TOXICITY

SPECIES	CONC. *	SYS. **	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Other	_____	_____	_____

ORAL TOXICITY

SPECIES	DOSE***	SYS. **	REF.
Man	_____	_____	_____
Rat	1454	LD ₅₀	_____
Mouse	861	LD ₅₀	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Cat	_____	_____	_____
Guinea Pig	_____	_____	_____
Other	_____	_____	_____

OTHER ROUTES OF ADMINISTRATION

SPECIES	ROUTE	DOSE***	SYS. **	REF.
1. Rabbit	Dermal	1782	mg/kg	_____
2.	_____	_____	_____	_____
3.	_____	_____	_____	_____
4.	_____	_____	_____	_____
5.	_____	_____	_____	_____
6.	_____	_____	_____	_____

* Concentration in mg/M³
 ** System for expression of toxicity
 *** Dose in mg/Kg
 † Revised 1973

JUSTIFICATION:

246

Data generated under contract between the Department of Transportation and the United States Air Force Toxic Hazards Laboratory.

Rat 14-Day Oral LD₅₀ = 1454 mg/kg
95% Confidence Limits (563-3550)

Mouse 14-Day Oral LD₅₀ = 561 mg/kg
95% Confidence Limits (456-677)

Rabbit 14-Day Dermal LD₅₀ = 1782 mg/kg
(24-Hour Skin Contact) 95% Confidence Limits (959-3336)

Data fall in the "Toxic" category.

TOXICITY DATA SHEET

COMPOUND: ALLYL ISOTHIOCYANATE

CODE: 249

CLASSIFICATION: HIGHLY TOXIC

INHALATION TOXICITY

SPECIES	CONC. *	SYS. **	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Other	_____	_____	_____

ORAL TOXICITY

SPECIES	DOSE***	SYS. **	REF.
Man	_____	_____	_____
Rat	488	LD50	_____
Mouse	308	LD50	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Cat	_____	_____	_____
Guinea Pig	_____	_____	_____
Other	_____	_____	_____

OTHER ROUTES OF ADMINISTRATION

	SPECIES	ROUTE	DOSE***	SYS. **	REF.
1.	Rabbit	Dermal	88	LD50	_____
2.	_____	_____	_____	_____	_____
3.	_____	_____	_____	_____	_____
4.	_____	_____	_____	_____	_____
5.	_____	_____	_____	_____	_____
6.	_____	_____	_____	_____	_____

* Concentration in mg/M³
 ** System for expression of toxicity
 ***Dose in mg/Kg

JUSTIFICATION:

249

Data generated under Contract between the Department of Transportation and the United States Air Force Toxic Hazards Laboratory.

Rat 14-Day Oral LD₅₀ = 488 mg/kg
95% Confidence Limits (235-1010)

Mouse 14-Day Oral LD₅₀ = 308 mg/kg
95% Confidence Limits (194-688)

Rabbit 14-Day Dermal LD₅₀ = 88 mg/kg
(24-Hour Skin Contact) (no confidence limits)

Data fall in "Toxic" category by oral exposure and in the "Highly Toxic" classification by the dermal route. Since transportation accidents may readily produce dermal exposures allyl isothiocyanate is classified as "Highly Toxic."

TOXICITY DATA SHEET

COMPOUND: ETHYL CHLOROACETATE

CODE: 250

CLASSIFICATION: TOXIC

INHALATION TOXICITY

SPECIES	CONC.*	SYS.**	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Other	_____	_____	_____

ORAL TOXICITY

SPECIES	DOSE***	SYS.**	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Cat	_____	_____	_____
Guinea Pig	_____	_____	_____
Other	_____	_____	_____

OTHER ROUTES OF ADMINISTRATION

SPECIES	ROUTE	DOSE***	SYS.**	REF.
1. Rabbit	Dermal	255	LD50	
2.				
3.				
4.				
5.				
6.				

- * Concentration in mg/M³
- ** System for expression of toxicity
- *** Dose in mg/Kg

JUSTIFICATION:

250

Data generated under contract between the Department of Transportation and the United States Air Force Toxic Hazards Laboratory.

Rabbit 14-Day Dermal LD₅₀ = 255 mg/kg
(24-Hour Skin Contact) 95% Confidence Limits (118-246)

Data fall in the "Toxic" category.

TOXICITY DATA SHEET

COMPOUND: METHYL ISOTHIOCYANATE

CODE: 251

CLASSIFICATION: HIGHLY TOXIC

INHALATION TOXICITY

SPECIES	CONC.*	SYS.**	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Other	_____	_____	_____

ORAL TOXICITY

SPECIES	DOSE***	SYS.**	REF.
Man	_____	_____	_____
Rat	218	LD ₅₀	_____
Mouse	106	LD ₅₀	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Cat	_____	_____	_____
Guinea Pig	_____	_____	_____
Other	_____	_____	_____

OTHER ROUTES OF ADMINISTRATION

	SPECIES	ROUTE	DOSE***	SYS.**	REF.
1.	Rabbit	Dermal	33	LD ₅₀	
2.					
3.					
4.					
5.					
6.					

* Concentration in mg/M³
 ** System for expression of toxicity
 *** Dose in mg/Kg

JUSTIFICATION:

251

Data generated under contract between the Department of Transportation and the United States Air Force Toxic Hazards Laboratory.

Rat 14-Day Oral LD₅₀ = 218 mg/kg
95% Confidence Limits (108-443)

Mouse 14-Day Oral LD₅₀ = 106 mg/kg
95% Confidence Limits (38-300)

Rabbit 14-Day Dermal LD₅₀ = 33 mg/kg
(24-Hour Skin Contact) 95% Confidence Limits (18-64)

Data fall in the "Toxic" category by oral exposure and in the "Highly Toxic" category by the dermal route. Since transportation accidents may readily produce dermal exposures in ethyl isothiocyanate is classified as "Highly Toxic."

TOXICITY DATA SHEET

COMPOUND: METHYL ISOCYANATE

CODE: 252

CLASSIFICATION: TOXIC

INHALATION TOXICITY

SPECIES	CONC.*	SYS.**	REF.
Man			
Rat			
Mouse			
Dog			
Monkey			
Other			

ORAL TOXICITY

SPECIES	DOSE***	SYS.**	REF.
Man			
Rat	138	LD50	
Mouse	123	LD50	
Dog			
Monkey			
Cat			
Guinea Pig			
Other			

OTHER ROUTES OF ADMINISTRATION

	SPECIES	ROUTE	DOSE***	SYS.**	REF.
1.	Rabbit	Dermal	1796	LD50	
2.					
3.					
4.					
5.					
6.					

* Concentration in mg/M³
 ** System for expression of toxicity
 *** Dose in mg/Kg

JUSTIFICATION:

252

Data generated under contract between the Department of Transportation and the United States Air Force Toxic Hazards Laboratory.

Rat 14-Day Oral LD₅₀ = 138 mg/kg
95% Confidence Limits (55-343)

Mouse 14-Day Oral LD₅₀ = 123 mg/kg
95% Confidence Limits (78-195)

Rabbit 14-Day Dermal LD₅₀ = 1796 mg/kg
(24-Hour Skin Contact) 95% Confidence Limits (945-3411)

Data all fall in the "Toxic" category.

TOXICITY DATA SHEET

COMPOUND: PHENYL ISOCYANATE

CODE: 253

CLASSIFICATION: TOXIC

INHALATION TOXICITY

SPECIES	CONC. *	SYS. **	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Other	_____	_____	_____

ORAL TOXICITY

SPECIES	DOSE***	SYS. **	REF.
Man	_____	_____	_____
Rat	_____	_____	_____
Mouse	_____	_____	_____
Dog	_____	_____	_____
Monkey	_____	_____	_____
Cat	_____	_____	_____
Guinea Pig	_____	_____	_____
Other	_____	_____	_____

OTHER ROUTES OF ADMINISTRATION

SPECIES	ROUTE	DOSE***	SYS. **	REF.
1. Rabbit	Dermal	7127	LD50	
2.				
3.				
4.				
5.				
6.				

* Concentration in mg/M³
 ** System for expression of toxicity
 *** Dose in mg/Kg

JUSTIFICATION:

253

Data generated under contract between the Department of Transportation and
the United States Air Force Toxic Hazards Laboratory

Rabbit 14-Day Dermal LD₅₀ = 7127 mg/kg

(24-Hour Skin Contact) 95% Confidence Limits (3744-13,535)

Data fall in "Toxic" category.

APPENDIX B

<u>Chemical</u>	<u>Statement of Purity</u>	<u>Source</u>	<u>Lot Number</u>
Cresol, mixed	National Formulary	J. T. Baker	36598
Allyl Isothiocyanate	BP 150-152°C	MCB*	5108
Methyl Isothiocyanate	MP 35-36°C	MCB	10300
Methyl Isocyanate	BP 37-39°C	MCB	9641
Phenyl Isocyanate	BP 60-62°C/20 mm	MCB	6088
Ortho-Nitroaniline	MP 71-72°C	MCB	2786
Ethyl Chloroacetate	BP 142-144°C	MCB	5635

*Matheson, Coleman & Bell

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