

Celanese Ltd.
1601 West LBJ Freeway
Dallas, TX 75234

Celanese

Telephone: 972-443-4000

PR 4565
8EHQ - 0398 - 14132

February 27, 1998
DBP-004-98

Contains No CBI

CERTIFIED MAIL RECEIPT # Z 148 387 713

This submission contains no confidential business information.

Attn: TSCA Section 8(e) Coordinator
Document Processing Center (TS-790)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460



8EHQ-98-14132

Dear Sir or Madam:

In accordance with the requirement of TSCA Section 8(e), Celanese, Ltd. hereby submits a final report for a subacute oral toxicity study of 3-Dimethylaminopropylamine (CAS No. 109-55-7) in the male and female rat.

Groups of male and female rats received 3-Dimethylaminopropylamine by oral gavage at dose levels of 0, 10, 50 or 250 mg/kg body weight per day for 28 days and were necropsied on day 29. OECD Guideline 407 was followed.

Intercurrent mortality occurred in four of ten females of the high dose group. The following clinical signs were observed in female animals of the high dose group sporadically between day 11 and 24 of the study: decreased spontaneous activity, stilted gait, swollen abdomen as well as impaired respiration. The clinical signs were mainly seen in those females which died intercurrently. One male animal of the high dose group showed clinical signs of respiratory effects at day 11 and 12 of the study.

Histopathologic examination revealed lesions in the four females of the high dose group dying intercurrently. These lesions (e.g., pulmonary edema/hemorrhage) were consistent with cardiorespiratory failure as cause of death. In addition, one of these females exhibited effects on the spleen and associated lymphoid tissue. In the one high dose male rat which had shown clinical signs, degeneration of the squamous epithelium of the forestomach was found.



88980000101

Hoechst

Celanese
A member of the Hoechst Group

59 MAR -9 AM 11:30
RECEIVED
OPPT/MCIC

59 MAR -9 AM 11:16
RECEIVED
OPPT/MCIC

February 27, 1998

DBP-004-98

Page 2

In conclusion, 3-Dimethylaminopropylamine caused clinical symptoms and mortality in rats when administered 28 times during 29 days at the dose level of 250 mg/kg body weight. The female rats seem to be more sensitive.

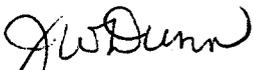
No compound-related adverse effects were observed in rats of either sex after repeated administration of 3-Dimethylaminopropylamine at the dose levels of 10 and 50 mg/kg body weight per day.

3-Dimethylaminopropylamine is a corrosive material and oral exposure to the high dose used in this study is not a likely exposure scenario. However, we are providing this information in accordance with previous EPA TSCA 8(e) guidance on repeated exposure studies.

This submission contains no confidential business information.

If any further information is required, do not hesitate to contact Debra Phillips, Coordinator, Product Stewardship at 972-443-4703.

Sincerely,



Jerry Dunn
Vice President, Environmental, Health, and Safety
Celanese

Enclosure

File: Log No. 1

3-Dimethylaminopropylamin

Testing for subacute oral toxicity
(28 applications within 29 days)
in the male and female Wistar rat

Author:	Dr. D. Bury
Report number:	96.0636
Date of report:	September 11, 1996
Study number:	95.0396
Origin of report:	Hoechst Marion Roussel Preclinical Development Drug Safety 65926 Frankfurt am Main GERMANY

1 SUMMARY / ABSTRACT.....	4
2 STATEMENT.....	6
2.1 GLP Compliance Statement.....	6
3 OBJECTIVE / GUIDELINES.....	7
3.1 Objective.....	7
3.2 Guidelines.....	7
4 SURVEY.....	8
4.1 Responsibilities.....	9
5 MATERIAL AND METHODS.....	10
5.1 Test compound.....	10
5.2 Test system.....	11
5.3 Test groups.....	12
5.4 Preparation of the test compound.....	12
5.5 Treatment schedule.....	13
6 OBSERVATIONS AND MEASUREMENTS.....	13
6.1 Behavior and state of health.....	13
6.2 Body weight.....	13
6.3 Food and water consumption.....	13
6.4 Hematological investigations.....	14
6.5 Clinical chemistry.....	15
6.6 Urine analysis.....	16
6.7 Necropsy and macroscopic examination.....	16
6.8 Organ weights.....	17
6.9 Histopathology.....	17
6.10 Statistics.....	17
7 RESULTS.....	18
7.1 Behavior, state of health and mortality.....	18
7.2 Body weight gain.....	18
7.3 Food and water consumption.....	19
7.4 Hematological investigations.....	19
7.5 Clinical chemistry.....	20
7.6 Urine analysis.....	20
7.7 Organ weights.....	20
7.8 Macroscopic and microscopic findings.....	21
8 CONCLUSION.....	22

APPENDIX	23
PATHOLOGY REPORT.....	23
FIGURES.....	80
Body weight development	80
Food consumption	82
Water consumption	84
SUMMARY TABLES AND STATISTICS	86
Clinical observations	86
Body weight development - statistics.....	118
Body weight development and food consumption - summary	122
Water consumption	138
Hematological investigations	140
Clinical chemistry.....	148
Urine analysis	154
Organ weights	156
INDIVIDUAL DATA	162
Body weight development and food consumption	162
Water consumption	243
Hematological investigations	245
Clinical chemistry.....	276
Urine analysis including legend	300
Organ weights	322
LIST OF TERMS USED IN THE TABLES	342
RANDOMIZATION TABLES	343
LIST OF METHODS.....	346
COMPOSITION OF DIET.....	355
HOMOGENEITY AND STABILITY OF THE TEST COMPOUND.....	356
QUALITY ASSURANCE STATEMENT	359

1 SUMMARY / ABSTRACT

Groups of 5 male and 5 female Wistar rats received 3-Dimethylaminopropylamin by oral gavage at dose levels of 0, 10, 50 or 250 mg/kg body weight per day for 28 days and were necropsied on day 29.

Because 3 females of the 250 mg/kg body weight group died during the study period, 5 females received 3-Dimethylaminopropylamin at the dose level of 250 mg/kg body weight per day for 28 days again and were necropsied on day 29.

Behavior and state of health were observed daily in all groups. Body weights and food consumption were recorded twice weekly, and water consumption once weekly.

Hematological examinations, clinical chemistry and urine analysis were carried out at the termination of the study.

During necropsy the animals were examined for macroscopically visible abnormalities, the main organs weighed and the organ to body weight ratios calculated. Many organs and tissues were processed for histopathological examination and checked for microscopically visible changes.

Body weights, hematological and clinical chemistry data, urine data (volume, pH value, specific weight), absolute and relative organ weights were analyzed with the aid of a statistical program to show differences compared with the controls.

Intercurrent mortality occurred in four of ten females of the high dose group.

One male animal of the high dose group showed irregular respiration as well as respiratory sounds at day 11 and 12 of the study. The following clinical signs were observed in female animals of the high dose group sporadically between day 11 and 24 of the study: decreased spontaneous activity, stilted gait, swollen abdomen as well as impaired respiration. The clinical signs were mainly seen in those females which died intercurrently. Behavior and state of health remained unaffected by the administration of the test compound in all other dose groups.

Body weight development, food and water consumption remained unaffected by the administration of the test compound in all groups.

No treatment-related changes were detected by urine analysis.

Hematological and clinical chemistry examinations did not show any compound-related effect.

Organ weights were not altered by the administration of the test compound.

No compound related gross findings were observed in terminally killed animals of all dose groups. The four high dose female rats which died intercurrently showed macroscopically visible changes such as discoloration of lungs with multiple red spots on its surfaces and foamy content. One of them also showed a small spleen.

Histopathological examinations revealed lesions in the four females of the high dose group dying intercurrently. These lesions included congestion of organs, pulmonary hemorrhage, and edema, consistent with cardiorespiratory failure as cause of death. In addition, one of these females exhibited marked loss of lymphatic follicles of the spleen with massive marginal zone and periarteriolar lymphoid sheath atrophy. In the one high dose male rat which had shown clinical signs, focal ballooning degeneration of the squamous epithelium of the forestomach was found.

In conclusion 3-Dimethylaminopropylamin caused clinical symptoms and mortality in male and female Wistar rats when administered 28 times during 29 days at the dose level of 250 mg/kg body weight. The female rats seem to be more sensitive.

No compound-related adverse effects were observed after repeated administration of 3-Dimethylaminopropylamin at the dose levels of 50 and 10 mg/kg body weight per day.

With regard to the present study the 'No Observed Adverse Effect Level' (NOAEL) is 50 mg/kg body weight per day.

2 STATEMENT

This report contains the unpublished research findings of Hoechst scientists. It should not be published, in whole or in part, or referred to in any publication without authorization from the company.

2.1 GLP Compliance Statement

This study was conducted in compliance with Good Laboratory Practice regulations: No unforeseen circumstances were observed which might have affected the quality or integrity of the study.

Study Director:

D. Bury September 17, 1996
(Dr. D. Bury)

Head of
Testing Facility:

h Mayer Sept. 12, 1996
(Dr. D. Mayer)

3 OBJECTIVE / GUIDELINES

3.1 Objective

The present 29-day toxicity study was conducted in order to characterize the toxicological profile of 3-Dimethylaminopropylamin after repeated oral exposure. Additionally, the results of this study can be used as a dose-range finding for subchronic and chronic toxicity studies.

3.2 Guidelines

The present study was conducted in compliance with

EEC-Guideline B.7. "Subacute Oral Toxicity" of the Directive 92/69/EEC: Commission Directive of July 31, 1992 adapting to technical progress for the seventeenth time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances

and

OECD Guidelines for Testing of Chemicals, 407 „Repeated Dose Oral Toxicity, Rodent: 28-day or 14-day Study" OECD 1981

This study was conducted in compliance with the

Principles of Good Laboratory Practice, annex of paragraph 19a, section 1 of the chemical law of July 25, 1994

Rationale for species selection: The Wistar rat has proved to be a suitable species for subacute oral toxicity testing with many different substances.

Rationale for the route of exposure: The oral route is considered to be a potential exposure route in man.

Rationale for dose-selection: In a dose range finding study groups of 3 male and 3 female Wistar rats received 3-Dimethylaminopropylamin at dose levels of 50 and 250 mg/kg body weight per day over a period of 14 days. The animals of the 50 mg/kg body weight group showed no clinical signs. The animals of the of the 250 mg/kg body weight showed sporadically swollen abdomen during the study period. Additionally, stilted gait were observed in one female animal. Development of body weight was not impaired. The animals killed at the end of the observation period showed no macroscopically visible changes.

Based on these results 3-Dimethylaminopropylamin was tested in the present study at the dose levels of 0, 10, 50 and 250 mg/kg body weight per day.

4 SURVEY

Study Number : 96.0396
Artemis Number : BR0139
Test compound : 3-Dimethylaminopropylamin
Sponsor : GB A, Werk Hoechst, Abt. TQM
Test system : Wistar rat / male and female
Route of administration : orally gavage
Duration of the study : 29 days, 28 applications
Start of the study : November 03, 1995
End of study : January 05, 1996

Dose levels and number of animals:

Group	Dose (mg/kg b.w.)	Number of animals	
		male	female
1	0	5	5
2	10	5	5
3	50	5	5
4	250	5	10

4.1 Responsibilities

Preclinical Development Drug Safety	:	Dr. D. Mayer
Industrial Toxicology	:	Dr. R. Jung
Study director	:	Dr. D. Bury
Laboratory diagnostics	:	Dr. H. H. Donaubaue
Pharma Development Corporate Pathology	:	Prof. Dr. K. H. Langer / Dr. M. Heinrichs
Pharma Informatic	:	Dr. H. Burghard / DM R. Uhl
Analytical Toxicology	:	Dr. H.-J. Pletsch
Quality Assurance (GLP)	:	S. J. Harston (Pharmacist)
Testing facility and archive	:	Hoechst Marion Roussel Preclinical Development Drug Safety 65926 Frankfurt am Main GERMANY

All raw data obtained in the course of the study are stored in accordance with the SOP.

5 MATERIAL AND METHODS

5.1 Test compound

Name	: 3-Dimethylaminopropylamin
Code	: IVT 005
Molecular formula	: $C_5H_{14}N_2$
Molecular weight	: 102.18 g/mol
Specific gravity	: 0.817 kg/L
Certificate of analysis	: of August 21, 1995
Appearance	: clear, colourless fluid
Melting point	: <-60 °C
Boiling point	: 135 °C (at 1013 hPa)
Solubility	: soluble in water > 10 g/L in polyethylene glycol 400 and ethanol
Batch number	: 8/95
Date of receiving	: August 28, 1995
Date of expiry	: August 21, 1996
Storage conditions	: darkness at room temperature in a fume cupboard
Stability and homogeneity in the vehicle	: is guaranteed for 4 hours

5.2 Test system

Species	: Wistar rat
Strain	: Hoe: WISKf(SPF71)
Origin	: Hoechst Aktiengesellschaft, Kastengrund, SPF breeding colony
Age at the start of the study	: approximately 6 weeks
Animal maintenance	: in fully air-conditioned rooms in macrolon cages (type 4) on soft wood granulate in groups of 5 animals
Room temperature	: $22 \pm 3^{\circ}\text{C}$
Relative humidity	: $50 \pm 20 \%$
Lighting time	: 12 hours daily
Acclimatization	: at least five days
Food	: ssniff [®] R/M-H (V 1534) ad libitum, except for the period in which the animals were kept in diuresis cages
Water	: tap water in plastic bottles ad libitum, except for the period in which the animals were kept in diuresis cages
Animal identification	: fur marking with KMnO_4 , numbered ear tags and cage numbering
Randomization	: computer-generated algorithm (Randomization tables 95.0744 and 95.0745)

5.3 Test groups

At the beginning of the acclimatization period, the test animals were randomized and assigned to the following groups according the randomization tables No. 95.0744 and 95.0745 (see page 343 and 344):

Group	Dose (mg/kg b.w.)	Number of animals		Animal number	
		male	female	male	female
1	0	5	5	1 - 5	21 - 25
2	62.5	5	5	6 - 10	26 - 30
3	250.0	5	5	11 - 15	31 - 35
4	1000.0	5	10	16 - 20	36 - 45

Group	Cage number	Animal number	Cage number	Animal number
		male		female
1	1	1 - 5	5	21 - 25
2	2	6 - 10	6	26 - 30
3	3	11 - 15	7	31 - 35
4	4	16 - 20	8 - 9	36 - 45

5.4 Preparation of the test compound

Dose (mg/kg b.w.)	Concentration in % (w/v)	Volume applied (mL/kg b.w.)	Vehicle	Frequency of preparation
0	0.0	5	deionized water	-
10	0.2	5	deionized water	daily
50	1.0	5	deionized water	daily
250	5.0	5	deionized water	daily

The test compound was dissolved homogeneously in the vehicle by means of a magnetic stirrer.

After each measurement of the body weight, the calculation of the application volume was repeated.

5.5 Treatment schedule

Route of application	:	orally gavage
Vehicle	:	deionized water
Schedule	:	28 applications within 29 days, 7 days per week
Time of application	:	between 7.00 and 12.00 a.m.
Frequency of the preparation of the test substance	:	daily, immediately before treatment

6 OBSERVATIONS AND MEASUREMENTS

6.1 Behavior and state of health

The behavior and general health condition of the animals were observed once daily. The animals were examined weekly for neurological disturbances, opacity of the refracting media of the eyes, damage to the oral mucosa and impairment of dental growth.

6.2 Body weight

The body weights of all animals were determined before the start of the study and then twice weekly throughout the study.

6.3 Food and water consumption

Food consumption was determined continuously (2 times per week). The values on the printouts refer to the intervals between one measurement and the next. They are converted to the food consumption per 100 g body weight over a 24 hour period.

Water consumption was determined once weekly over a period of 16 hours and is given in the results as water consumption / animal / 16 h (from approx. 3.15 p.m. to 7.15 a.m.)

6.4 Hematological investigations

At the termination of the study, hematological examinations were performed on all animals without previous withdrawal of food. Blood samples were taken from the retroorbital venous plexus in narcosis (intraperitoneal injection of 50-100 mg Ketamin / kg body weight). In order to prevent systematic errors, blood sampling was conducted in a randomized order (randomization table No. 95.0746, see page 345).

The following hematological parameters were determined:

Parameter	Method
Erythrocyte count	1.1
Hemoglobin	1.2
Hematocrit	1.3
Mean corpuscular volume (MCV)	1.4
Mean corpuscular hemoglobin (MCH)	1.5
Mean corpuscular hemoglobin concentration (MCHC)	1.6
Leucocyte count	1.7
Thrombocyte count	1.8
Differential leucocyte count and red cell morphology	1.9
Reticulocyte count*	1.10
Heinz bodies*	1.11
Coagulation time	1.14.1

* These parameters were scored in the control group and high dose group only.

(For a description of the methods used see Appendix, page 346)

6.5 Clinical chemistry

After blood sampling for hematological testing, the animals were killed by section of the vena cava cranialis in deep narcosis and exsanguinated. In order to prevent systematic errors, exsanguination was conducted in a randomized order (randomization table No. 95.0746, see page 96.0345).

The following serum values were determined:

Parameter	Method
Sodium	2.1
Potassium	2.2
Inorganic phosphorus	2.3
Uric acid	2.4
Bilirubin total	2.5
Creatinine	2.7
Glucose	2.8
Urea	2.9
Calcium	2.10
Chloride	2.11
Aspartate aminotransferase (ASAT/GOT)	2.14
Alanine aminotransferase (ALAT/GPT)	2.15
Alkaline phosphatase (AP)	2.16
Gamma-glutamyltranspeptidase (GGT)*	2.18
Cholesterol	2.22
Triglycerides	2.23
Total protein	2.26
Albumin	2.30

* detection limit: 1 U/L

(For a description of the methods used see Appendix, page 349)

6.6 Urine analysis

Urine analysis was performed on all animals a few days before termination of the study. For this purpose, the urine was collected by using metabolism cages (overnight from day 26 to day 27). Food and water were withdrawn during this period.

The following parameters were checked:

Parameter	Method
Appearance	3.1
Color	3.1
pH-Value	3.2
Hemoglobin	3.2
Protein	3.2
Glucose	3.2
Ketone bodies	3.2
Bilirubin	3.2
Urobilinogen	3.2
Specific weight	3.4
Sediment	3.6.1
Volume	3.7

(For a description of the methods used see Appendix, page 352)

6.7 Necropsy and macroscopic examination

After exsanguination, all animals were necropsied and checked for macroscopically visible abnormalities. The autopsy included macroscopic examination of the skin, orifices, eyes, teeth, oral mucosa and internal organs.

All abnormal findings were recorded.

6.8 Organ weights

The following organs were weighed and the organ to body weight ratios calculated:

Heart	Spleen
Liver	Adrenals
Kidneys	Testes
Ovaries	Epididymides
Lungs	

6.9 Histopathology

The following tissues or organs (or pieces of them) were preserved in a suitable fixative and processed for histopathological investigations:

Heart	Stomach
Liver	Jejunum
Kidneys	Colon
Adrenals	Uterus
Spleen	Ovaries
Testes	Epididymides
Lungs	

6.10 Statistics

The following parameters were compared statistically with the control group values at the level of significance $p = 0.05$:

- Body weights at the designated measurement times
- Hematological data
- Clinical chemistry parameters
- Urine analysis (Volume, pH-value and specific weight)
- Absolute organ weights and organ to body weight ratios

Evaluation was performed by Pharma Informatics with the aid of a program package for the evaluation of toxicological studies. The calculation methods used are referred to on the computer printouts.

7 RESULTS

7.1 Behavior, state of health and mortality

Mortality occurred in four females of the 250 mg/kg body weight group. The animals were found dead on days 11, 18, 22 and 25 of the study.

One male animal of the high dose group showed irregular respiration as well as respiratory sounds at day 11 and 12 of the study. The following clinical signs were observed in female animals of the high dose group sporadically between day 11 and 24 of the study: decreased spontaneous activity, stilted gait, swollen abdomen, respiratory sounds, gasping and panting. The clinical signs were mainly seen in those females which died intercurrently. Behavior and state of health remained unaffected by the administration of the test compound in all other dose groups.

Compound-related neurological disturbances, opacity of the refracting media of the eyes, impairment of dental growth or changes of the oral mucosa were not observed.

(Summary tables see page 86)

7.2 Body weight gain

Body weight development was not impaired by the administration of the test compound and was comparable in all groups.

(Figures page 80, Statistics page 118, Summary tables page 122, Individual data page 162)

7.3 Food and water consumption

Absolute and relative food consumption remained unaffected by the administration of the test compound throughout the study.

(Figures page 82, Summary tables page 122, Individual data page 162)

Likewise, the administration of the test compound did not alter the water consumption.

(Figures page 84, Summary tables page 138, Individual data page 243)

The mean food and water consumption throughout the study were as follows:

Treatment group	Food consumption (g/100 g b.w./day)		Water consumption (g/animal/day)	
	males	females	males	females
Control	9.99	9.36	30.2	23.7
10 mg/kg b.w.	9.93	9.51	30.3	23.1
50 mg/kg b.w.	10.08	9.45	29.0	22.4
250 mg/kg b.w.	9.85	9.57	28.1	23.7

7.4 Hematological investigations

Hematological examinations revealed statistically significant decreases in erythrocyte counts as well as in hemoglobin and hematocrit values in males of the intermediate dose group. Haematocrit values were also decreased in males of the high dose group. Leukocyte counts were statistically significantly decreased in males of the intermediate and females of the low dose group. In all cases there was no dose dependency or the values were within the physiological range of rats. Therefore, a compound-related effect is not evident.

(Summary tables and Statistics page 140, Individual data page 245).

7.5 Clinical chemistry

Statistical evaluation revealed increases in aspartate aminotransferase and decreases in total protein values in females from the high dose group. Inorganic phosphorus values were decreased in females of the low dose group. Males of the intermediate dose group showed statistically significant decreases in total bilirubin values. In all dose groups of the females the uric acid values were statistically significantly decreased. In all cases there was no dose dependency or the values were within the physiological range of rats. Therefore, a compound-related effect is not evident.

(Summary tables and Statistics page 148, Individual data page 276)

7.6 Urine analysis

Examination of the urine did not reveal any abnormalities.

The sediments were inconspicuous.

(Summary tables page 154, Individual data page 300, Legend for the urinary findings page 320).

7.7 Organ weights

In males of the intermediate dose group statistical evaluation of the organ weights revealed increases in relative liver weights. As there was no dose dependency a compound-related effect is not evident.

(Summary tables and Statistics page 156, Individual data page 322)

7.8 Macroscopic and microscopic findings

In terminally killed animals, no macroscopically visible organ alterations attributable to the compound administration were observed. Dilatation of renal pelvices was found in some male or female animals of all treatment groups and therefore was not considered to be compound-related but to be a strain specific alteration.

In the four high dose females which died intercurrently gross findings included discoloration of lungs with multiple red spots on its surfaces and foamy content. One female also showed a small spleen.

Histopathological examinations revealed lesions in the four females of the high dose group dying intercurrently. These lesions included congestion of organs, pulmonary hemorrhage, and edema, consistent with cardiorespiratory failure as cause of death. In addition, one of these females exhibited marked loss of lymphatic follicles of the spleen with massive marginal zone and periarteriolar lymphoid sheath atrophy, probably reflecting chronic stress due to treatment. In the one high dose male rat which had shown clinical signs, focal ballooning degeneration of the stratum corneum of the squamous epithelium of the forestomach with granulocytic infiltration of the submucosa was found, most likely due to the locally irritating effect of the compound.

Details are given in the report of the Dept. for Experimental Pathology (Dr. Heinrichs, Prof. Dr. Langer, page 23).

8 CONCLUSION

In conclusion, 3-Dimethylaminopropylamin caused clinical symptoms and mortality in male and female Wistar rats when administered 28 times during 29 days at the dose level of 250 mg/kg body weight. The female rats seem to be more sensitive.

No compound-related adverse effects were observed after repeated administration of 3-Dimethylaminopropylamin at the dose levels of 50 and 10 mg/kg body weight per day.

With regard to the present study the 'No Observed Adverse Effect Level' (NOAEL) is 50 mg/kg body weight per day.

Dr. BU / LW / GL

Quality Assurance (GLP)

Uhu, 24.8.96

R. Jung 16. Sept. 1996
Dr. R. Jung
Industrial Toxicology

Hoechst Marion Roussel
Preclinical Development
Drug Safety

D. Bury September 11, 1996
Dr. D. Bury
Study Director

K.H. Langer Sept. 19, 1996
Prof. Dr. K. H. Langer
Pharma Development
Corporate Pathology

W. Mayer Sept 11, 1996
Dr. D. Mayer
Preclinical Development
Drug Safety