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APPENDIX 3

Robust Summaries for Petroleum Gases
Consortium Registration #

Explanatory Note for Robust Summary Format

The Petroleum HPV Testing Group has elected to use the IUCLID (International Uniform Chemical Information Database) as the repository for robust summaries for the program. IUCLID has been structured to accommodate a wide variety of data so that it can be used as a repository for all available data on any given chemical or category of chemicals. Many of the data elements (*e.g.*, OECD company location and production information, packaging information, emergency procedures, etc.) are outside the SIDS (Screening Information Data Set) requirements of the US HPV Chemical Challenge. Consequently, only those fields relevant to existing data and proposed testing in support of the Petroleum Gases Test Plan are presented in this document.

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**ROBUST SUMMARY
OF INFORMATION ON**

Substance Group: PETROLEUM GASES

Summary prepared by: American Petroleum Institute

Creation date: 02 NOVEMBER 1999

Printing date: 29 AUGUST 2001

Date of last Update: 03 OCTOBER 2001

NB. Reliability of data included in this summary has been assessed using the approach described by Klimisch, et al.

Klimisch, H. J., Andreae, M. and Tillman, U. (1997)

A systematic approach for evaluating the **quality** of experimental toxicological and ecotoxicological data.
Regulatory Toxicology and Pharmacology **25**, 1-5.

1. General Information

Id Gases
Date 03.10.2001

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : petroleum product
Physical status : **gaseous**
Remark : Petroleum gases are obtained from natural **gas** processing and petroleum refining operations. They are typically Class II substances on the TSCA Inventory which are "Chemical Substances of Unknown or Variable Composition, Complex Reaction Products, and Biological Materials." Their properties may be assessed from a consideration of the properties of the individual components.

This summary includes the available information on the following components:

Methane
Ethane
Propane
normal Butane
iso-Butane

Where available, physico-chemical data are also included for normal and **iso-pentane**.

For information on published reviews of information available on other individual hydrocarbons which may be components of petroleum gas see section 1.17.

1.2 SYNONYMS

Petroleum gas
Liquefied petroleum gas
LPG

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : TLV (US)
Limit value : 1000 other: ppm
Short term exposure
Limit value : None established
Schedule : 8 hour(s)
: In addition to the TLV established for LPG by the ACGIH, exposure limits have also been established for the following hydrocarbons likely to be present in petroleum gas:

| | | |
|-----------------------|----------|---|
| Methane | No TLV | listed as a simple asphyxiant |
| Ethane | No TLV | listed as a simple asphyxiant |
| Propane | 2500 ppm | critical effect simple asphyxiant |
| Butane | 800 ppm | critical effect narcosis |
| Pentane (all isomers) | 600 ppm | critical effects irritation and narcosis. |

(3)

1.17 REVIEWS

: There have been several reviews of the information available on various components of the petroleum gas group. These are as follows:

| | |
|---------------------------|---------------------------------|
| n-Pentane | McKee, et al. (1998) |
| 1,3-butadiene | EU (1999) and CMA (1999) |
| 9 individual hydrocarbons | Mackerer and Galvin 1999 |

In addition, the report of a safety assessment of isobutane, isopentane, n-butane and propane with respect to usage as aerosol propellants in cosmetics has also been published (Anon, 1982).

The FDA has listed Propane, n-Butane and **iso-Butane** as GRAS (Generally **Recognised** As Safe) substances (21 CFR 184.1655 and 21 CFR 184.1165)

A scientific literature review of GRAS substances has been published, and this included information on propane, n-butane and **iso-butane** (NTIS, 1974). It should be noted that some of the information included in the scientific literature review has not been included in the robust summary. However, no data have been omitted that are considered to be significant.
(1) (2) (4) (12) (15) (28) (30) (31)

2. Physico-Chemical Data

Id Gases
Date 03.10.2001

2.1 MELTING POINT

Value : -189.7 - -130 °C
Decomposition : no
Sublimation : no
GLP : no data
: Values given above span the range of values for the individual hydrocarbons that may be present in Petroleum gas.
Values for the individual hydrocarbons are as follows:
Methane -182°C
Ethane -183.3%
Propane -189.7%
n-Butane -138.4°C
iso-Butane -159.4%
n-Pentane -130°C
iso-Pentane -159°C
Reliability : (1) valid without restriction
Data are taken from the CRC Handbook of chemistry and physics

(13)

2.2 BOILING POINT

Value : -164 - -.5 °C
Decomposition : no
GLP : no data
: Values given above span the range of values for the individual hydrocarbons that may be present in Petroleum gas.
Values for the individual hydrocarbons are as follows:
Methane -164°C
Ethane -88.6%
Propane -42.1 °C
n-Butane -0.5%
iso-Butane -11.7%
n-Pentane -36.1 °C
iso-Pentane -27.8%
Reliability : (1) valid without restriction
Data are taken from the CRC Handbook of chemistry and physics

(13)

2. Physico-Chemical Data

Id Gases
Date 03.10.2001

2.3 DENSITY

Type : relative density
Value : 0.3 - 0.584
GLP : no data
: Relative densities given above span the range of values for the individual hydrocarbons (liquid) that may be present in Petroleum gas.
Relative densities (**15/1 5°C**) of the individual liquid hydrocarbons are:
Methane 0.3 (estimated)
Ethane 0.35619
Propane 0.50698
n-Butane 0.58402
iso-Butane 0.56286
n-Pentane 0.63108

Reliability : (4) not assignable

(17)

2.3.1 GRANULOMETRY

: Not relevant

2.4 VAPOUR PRESSURE

Value : 5309 - 350000 hPa
GLP : no data
: Values given above span the range of values for the individual hydrocarbons that may be present in Petroleum gas.
Values for the individual hydrocarbons are shown below.
The units are given as hPa(abs) @ **313.15K**
Methane 350000 (estimated)
Ethane 60000 (estimated)
Propane 13698
n-Butane 3796.1
iso-Butane 5308.9
n-Pentane 1147
iso-Pentane 1513.1

Reliability : (4) not assignable

(17)

2.5 PARTITION COEFFICIENT

Log pow : ≤ 2.3 at ° C
Year : 1987
GLP : no data
: Measured values have been taken from the Pomona College Log P Data Base.
Log P values for the individual hydrocarbons that may be present in Petroleum gas are:
Methane 1.09
Ethane 1.81
Propane 2.3
n-Butane 2.8
iso-Butane 2 . 8

Reliability : (4) not assignable

Data taken from an on-line database.

23.04.2001

(19) (20) (35)

2. Physico-Chemical Data

Id Gases
Date 03.10.2001

2.6.1 WATER SOLUBILITY

Year : 1966
: McAuliffe reports the following water solubilities:

| <u>Substance</u> | <u>Solubility (mg/l)</u> |
|------------------|--------------------------|
|------------------|--------------------------|

| | |
|-----------|------|
| Methane | 24 |
| Ethane | 60 |
| Propane | 62 |
| Butane | 61 |
| Isobutane | 48.9 |

Reliability : (2) valid with restrictions

(29)

2.7 FLASH POINT

Value : ca. -60 ° C
GLP : no data

: Flash points for the individual hydrocarbons that may be present in Petroleum gas are as follows:

| <u>Hydrocarbon</u> | <u>Flash Point (°C)</u> |
|--------------------|-------------------------|
|--------------------|-------------------------|

| | |
|-------------------|--------------|
| Methane | -187.78 |
| Ethane | -135 |
| Propane | -104.44 |
| n-Butane | -60 |
| iso-Butane | -82.7 |

Reliability : (4) not assignable

(34)

2.8 AUTO FLAMMABILITY

Value : 410 - 540" c
GLP : no data

: Autoignition temperatures for the individual hydrocarbons that may be present in Petroleum gas are as follows:

| <u>Hydrocarbon</u> | <u>Autoianition Temperature (°C)</u> |
|--------------------|--------------------------------------|
|--------------------|--------------------------------------|

| | |
|-------------------|------------|
| Methane | 540 |
| Ethane | 515 |
| Propane | 450 |
| n-Butane | 405 |
| iso-Butane | 462 |

Reliability : (4) not assignable

(26)

2.9 FLAMMABILITY

: extremely flammable

2.10 EXPLOSIVE PROPERTIES

: **UELs** and **LELs** for the individual hydrocarbons that may be present in Petroleum gas are as follows:

| | LEL (%vol.) | UEL (%vol.) |
|---------------------|----------------|----------------|
| Methane | 5.0 | 15 |
| Ethane | 3.0 | 12.5 |
| Propane | 2.12 | 9.35 |
| N-Butane | 1.86 | 8.41 |
| iso-Butane 1 | .8 | 8.44 |
| n-Pentane | 1.4 | 7.8 |
| iso-Pentane | 1.32 | |

Reliability

: (1) valid without restriction
Data are taken from the CRC Handbook of chemistry and physics

(13)

3. Environmental Fate and Pathways

Id Gases
Date 03.10.2001

3.1 .1 PHOTODEGRADATION

Type : air
Method : Calculated according to Atkinson 1990
GLP : no
: Atkinson gives rate constants which enable half lives to be calculated for degradation of hydrocarbons in contact with hydroxyl radicals in the troposphere, under the influence of sunlight. The calculated half lives for the components of petroleum gas are as follows:

| <u>Constituent</u> | <u>Half Life (Days)</u> |
|--------------------|-------------------------|
| Methane | 960 |
| Ethane | 30 |
| Propane | 7 |
| isobutane | 3.4 |
| n-butane | 3.2 |

Reliability : (4) not assignable
Calculations were made using the constants listed in reference by Atkinson.

(7)

3.1.2 STABILITY IN WATER

: The C₁ to C₄ alkanes are relatively inert, nonpolar, hydrophobic substances that do not react with water or hydroxide ions. Reactivity with water does not occur due to the high bond dissociation energy and nonelectronegativity of the carbon-hydrogen bonds, characteristic of alkanes. Therefore, alkanes are not hydrolytically reactive.

(21)

3.1.3 STABILITY IN SOIL

: See comment in section 3.8

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

: In the event of an accidental release of any of the C₁ to C₄ hydrocarbons to the environment, all of the material will end up in the air compartment due to the volatility of the hydrocarbons.

3.3.2 DISTRIBUTION

Media : air ▪ biota ▪ sediment(s) ▪ soil ▪ water
Method : Calculation according Mackay, Level I
Method : Distribution has been calculated according to Mackay Level 1. using parameters defined by van der Zandt and van Leeuwen.
Result : Results for the C₁ to C₄ hydrocarbons are as follows:

| <u>Air</u> | <u>Water</u> | <u>Soil</u> | <u>Sediment</u> | <u>Suspended</u> | <u>Biota</u> |
|------------|--------------|-------------|-----------------|-------------------|--------------|
| <u>(%)</u> | <u>(%)</u> | <u>(%)</u> | <u>(%)</u> | <u>matter (%)</u> | <u>%</u> |
| 100 | 0 | 0 | 0 | 0 | 0 |

(27) (39)

3. Environmental Fate and Pathways

Id Gases
Date 03.10.2001

: EQC multimedia modeled Level 1 estimates for transport/distribution have been prepared for methane, ethane, propane, butane and isobutane. These estimates are included as attached documents in corresponding IUCLID files.

3.4 MODE OF DEGRADATION IN ACTUAL USE

: Petroleum gases used as fuels are burnt to yield mainly carbon dioxide, carbon monoxide and water vapor. When the unburnt hydrocarbons enter the atmosphere they are photodegraded by reaction with hydroxyl radicals. See section 3.1 .1.

(6)

3.5 BIODEGRADATION

Type : aerobic
Inoculum : other: adapted microorganisms
Degradation Result : **76.2** % after 35 days
Method : inherently biodegradable
Year : 1963
GLP : no data
Test substance Method : Methane
: The 35-day BOD was determined at 25°C using 1 .0 mg of methane and mixed cultures of hydrocarbon oxidizing bacteria. The hydrocarbon was dispersed in the BOD solution by adsorption on ignited sand.
No further details of the test method are provided.
Remark : Biodegradation of C₁ through C₅ alkanes may occur in soil and water; however, volatilization is expected to be a far more important fate process in water. These gases are expected to exist entirely in the vapor phase in the ambient atmosphere. Reaction with hydroxyl radicals is the major sink for these hydrocarbon gases.
Reliability : (4) not assignable
Insufficient information given in the publication.

(22) (43)

3. Environmental Fate and Pathways

Id Gases
Date 0310.2001

Type : aerobic
Inoculum : other: adapted microorganisms
Degradation Result : 65.7 % after 35 days
Year : 1963
GLP : no data
Test substance Method : Ethane
: The 35-day BOD was determined at 25°C using 1 .0 mg of ethane and mixed cultures of hydrocarbon oxidizing bacteria. The hydrocarbon was dispersed in the BOD solution by adsorption on ignited sand.
No further details of the test method are provided.
Reliability : (4) not assignable
Insufficient information given in the publication.

(43)

3.8 ADDITIONAL REMARKS

: The ability of bacteria to use C₁ to C₄ hydrocarbons as a carbon source has been demonstrated in a number of studies.

Fuerst & Stephens demonstrated that *Methylococcus* and other cultures were able to use methane as a carbon source. Also, organisms such as *Neurospora crassa* were able to grow utilizing ethane.

Stephens, et al., have also shown that butane supports the growth of *N. crassa*.

O'Brien & Brown showed that both butane and iso-butane support growth of *Mycobacterium phlei*, and also that butane supports the growth of *Mycobacterium crassa*.

Vestal and Perry found that ethane, propane, and butane promoted the growth of *Mycobacterium vaccae*, suggesting that these hydrocarbons are biodegradable.

In contrast, studies by Wanatabe & Takesue and by Rode & Foster have shown that butane is also able to inhibit the growth of certain bacteria, moulds, fungi and plant seeds.

Gaseous alkanes are widespread in nature, and numerous types of microbes have evolved which are capable of oxidizing these substances as sole energy and carbon sources. A number of bacterial and eukaryotic species which can grow on gaseous alkanes have been isolated from a variety of soil, water and sediment environments. Although volatilization is the predominant behavior for these gases, sufficient aqueous solubility and subsequently bioavailability is exhibited by these alkanes which can serve as substrates for microbial metabolism. The use of gaseous carbon sources for cell growth is common among autotrophic organisms, although growth rates of gaseous hydrocarbons can be somewhat long. Generation times can be from 4 to 24 hours, but the cell yield can be somewhat high in comparison to C₁ through C₄ alcohols, esters, and carboxylic acids.

(16) (32) (33) (37) (40) (41) (42)

4. Ecotoxicity

Id Gases
Date 03.10.2001

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : Predicted value for fish acute toxicity
Exposure period : 96 hour(s)
Unit : mg/l
Method : ECOSAR modelling
Results : ECOSAR predicted fish acute toxicity values have been estimated as follows using measured water solubility values and calculated and measured Log P:

| <u>Substance</u> | <u>96-Hr. LC₅₀ (mg/l)</u> |
|------------------|--------------------------------------|
|------------------|--------------------------------------|

| | |
|-----------|---------|
| Methane | 166.759 |
| Ethane | 97.126 |
| Propane | 49.319 |
| Butane | 22.027 |
| Isobutane | 11.26 |

Reliability : (2) Reliable with restrictions
Remark : Estimated toxicity values for these gases should be considered reliable with restrictions, as the gaseous chemicals are not represented in the ECOSAR program by test data for surrogate chemicals. Given the water solubility and vapor pressure properties of these gases, multimedia modeling predicts these gases will not partition into water and persist at concentrations where adverse effects would be expected to occur.

Exposure period : 96 hour(s)
Unit : mg/l
TLM96 : > 1000 but no units given
GLP : no data
Test substance : Methane, propane & butane
Remark : The value is cited in Patty, but it has not been possible to obtain the original reference. The basis for this value, therefore, is not clear.

Reliability : (4) not assignable
This information is not reliable.

(34)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Predicted value for invertebrate 48-hour acute toxicity
Exposure period : 48 hour(s)
Unit : mg/l
Method : ECOSAR modelling
Results : ECOSAR predicted invertebrate acute toxicity 48-hour EC₅₀ values using measured water solubility values and calculated and measured Log P are:

| <u>Substance</u> | <u>48-hr. EC₅₀ (mg/l)</u> |
|------------------|--------------------------------------|
|------------------|--------------------------------------|

| | |
|-----------|---------|
| Methane | 164.244 |
| Ethane | 99.297 |
| Propane | 52.157 |
| Butane | 24.113 |
| Isobutane | 12.7 |

Reliability : (2) Reliable with restrictions
Remark : Estimated toxicity values for these gases should be considered reliable with restrictions, as the gaseous chemicals are not represented in the ECOSAR program by test data for surrogate chemicals. Given the water solubility and vapor pressure properties of these gases, multimedia

4. Ecotoxicity

Id Gases
Date 03.10.2001

modeling predicts these gases will not partition into water and persist at concentrations where adverse effects would be expected to occur.

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other aquatic plant: Predicted aquatic plant toxicity
Exposure period : 96 hour(s)
Unit : mg/l
Method : ECOSAR modelling
Results : ECOSAR predicted aquatic plant acute toxicity values using measured water solubility values and calculated and measured Log P have been estimated as follows:

| <u>Substance</u> | <u>96-hr. EC₅₀ (mg/l)</u> |
|------------------|--------------------------------------|
|------------------|--------------------------------------|

| | |
|-----------|--------|
| Methane | 95.717 |
| Ethane | 59.695 |
| Propane | 32.252 |
| Butane | 15.346 |
| Isobutane | 1.25 |

Reliability (2) Reliable with restrictions
Remark Estimated toxicity values for these gases should be considered reliable with restrictions, as the gaseous chemicals are not represented in the ECOSAR program by test data for surrogate chemicals. Given the water solubility and vapor pressure properties of these gases, multimedia modeling predicts these gases will not partition into water and persist at concentrations where adverse effects would be expected to occur.

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

: See section 5.5 below

5. Toxicity

Id Gases
Date 03.10.2001

5.1.1 ACUTE ORAL TOXICITY

Remark : Not applicable

5.1.2 ACUTE INHALATION TOXICITY

Type : LC₅₀
Species : rat
Sex : male/female
Number of animals : 6
Vehicle : substance administered with air
Exposure time : 15 minute(s)
Value : > 800000 ppm
Year : 1982
GLP : no data
Test substance : Propane, purity not specified
Test condition : Propane was passed through a calibrated rotameter and mixed with the required amount of air. As soon as the concentration of propane exceeded 25%, oxygen was mixed with the air to maintain an oxygen concentration of 20%.

Method : Groups of either 6 male or 6 female rats were exposed for 15 minutes in 500-ml., whole-body inhalation chambers. The animals were observed for effects on the CNS over a 10-minute exposure period. The EC₅₀ CNS effect concentration (10 mins) was calculated. The concentrations causing death after 15 minutes exposure were recorded and the LC₅₀ (15 mins) was calculated. A range of concentrations was used such that the no-effect concentration, the 100% effect concentration, and several in-between concentrations were determined. [Details of actual concentrations are not provided].

Result : Propane caused CNS depression. Signs of intoxication were: slight ataxia, loss of righting reflex, loss of movement, narcosis, shallow respiration and death eventually from respiratory depression. Recovery from a non-lethal exposure was rapid and the rats appeared normal within 10 minutes. Where deaths occurred, they were during exposure, never afterwards. The calculated EC₅₀ and LC₅₀ values with 95% confidence limits, expressed as concentrations in air (ppm), are as follows:

| | |
|---|--|
| EC ₅₀ (CNS depression, 10 mins.) | 280000 (220000-350000) [=504,996 (396,783-631,245)mg/m ³] |
| LC ₅₀ (15 mins.) | >800000 [=1,442,847 mg/m ³] |

Reliability : (2) valid with restrictions
Study not performed to guidelines and some experimental details lacking.

(11)

5. Toxicity

Id Gases
Date 03.10.2001

Type : LC₅₀
Species : rat
Sex : male/female
Number of animals : 6
Vehicle : other: substance administered with air
Exposure time : 15 minute(s)
Value : 570000 ppm
Year : 1982
GLP : no data
Test substance : Isobutane, purity not specified
Test conditions : Isobutane was passed through a calibrated rotameter and mixed with the required amount of air. As soon as the concentration of isobutane exceeded 25%, oxygen was mixed with the air to maintain an oxygen concentration of 20%.

Method : Groups of either 6 male or 6 female rats were exposed for 15 minutes in 500-ml., whole-body inhalation chambers. The animals were observed for effects on the CNS over a 10-minute exposure period. The EC₅₀ CNS effect concentration (10 mins) was calculated. The concentrations causing death after 15 minutes exposure were recorded and the LC₅₀ (15 mins) was calculated. A range of concentrations was used such that the no effect concentration, the 100% effect concentration, and several in-between concentrations were determined. [Details of actual concentrations are not provided].

Result : Isobutane caused CNS stimulation. Signs of intoxication were: slight tremors of the limbs, marked tremors of the limbs and head, convulsions, narcosis, shallow respiration and death from respiratory depression. Recovery from a non-lethal exposure was rapid and the rats appeared normal within 10 minutes. Where deaths occurred, they were during exposure, never afterwards. The calculated EC₅₀ and LC₅₀ values with 95% confidence limits, expressed as concentrations in air (ppm), are as follows:

| | |
|---|---|
| EC ₅₀ (CNS stimulation 10 mins.) | 200000 (160000-230000) |
| | [=475,444 (380,355-546,760)mg/m ³] |
| LC ₅₀ (15 mins.) | 570000 (480000-650000) |
| | [=1,355,015 (1,141,065-1,545,192) mg/m ³] |

Reliability : (2) valid with restrictions
Study not performed to guidelines and some experimental details lacking.

(11)

5. Toxicity

Id Gases
Date 03.10.2001

Type : LC₅₀
Species : rat
Sex : no data
Exposure time : 4 hour(s)
Value : 658 mg/l
Year : 1969
GLP : no data
Test substance : Butane, no further specification.
Method : Method not described, dose levels, group sizes, observation period not specified. LC₅₀ stated to be estimated by Litchfield & Wilcoxon method.

Result : Study was conducted to determine butane levels in several organs.
Butane was found in brain, kidney, liver and perinephric adipose tissue.

Reliability : (3) invalid
Study not performed to guidelines and some experimental details lacking.

(36)

Type : other
Species : rat
Strain : no data
Sex : male
Number of animals : 5
Year : 1984
GLP : no data
Test substance : The following aerosols of the solvents and propellants were tested :

| <u>Sample</u> | <u>Constituent</u> | <u>Concentration</u> |
|---------------|--|----------------------|
| 1 | Chlorothene P12 propellant Isobutane | 75% 25% 0% |
| 2 | Chlorothene P12 propellant Isobutane | 75% 10% 15% |
| 3 | Chlorothene P12 propellant Isobutane | 75% 5% 20% |
| 4 | Chlorothene P12 propellant Isobutane | 75% 0% 25% |

Additionally, samples of aerosols of Scotchguard fabric protector formulations were also tested. The formulations were:

| <u>Sample</u> | <u>Constituent</u> | <u>Concentration</u> |
|---------------|---|----------------------|
| F1 | FCR in Chlorothene Propellant P12 Isobutane | 75% 25% 0% |

5. Toxicity

Id Gases
Date 03.10.2001

| | | |
|-----------|----------------------|-----|
| F2 | FCR in NC1815 | 75% |
| | Propellant P12 | 10% |
| | Isobutane | 15% |
| F3 | FCR in NC1815 | 75% |
| | Propellant P12 | 5% |
| | Isobutane | 20% |
| F4 | FCR in NC1815 | 75% |
| | Propellant P12 | 0% |
| | Isobutane | 25% |

Method

The method used is an FDA recommended technique for aerosol propellants.

Five male rats were exposed under static conditions to an aerosol of the test material. In each test, the animals were subjected to 30 seconds of continuous spray and allowed to remain in the sprayed atmosphere for 15 minutes. During the next 15 minutes, the chamber was flushed with room air. The procedure was repeated at 30-minute intervals.

Two series of experiments were carried out. In the first series, each group of animals was subjected to 10 successive exposures within 5 hours. In the second series, the animals were subjected to only two exposures within one hour.

During the exposures, animals were observed for anesthesia, nasal irritation and other effects (unspecified in report). At the termination of the exposures, all animals were kept for 2 weeks.

Animals which succumbed were necropsied for gross pathological examinations. Survivors were also sacrificed for examination after 2 weeks.

Result

Studies with solvents and propellants alone (10 exposures)

There were no mortalities in these studies. Anesthesia was slight (aerosol containing no isobutane) and moderate in all the other test groups. Respiration was deep and rapid in all groups except the one containing no isobutane, and in this group no respiratory distress was observed. Following exposure to the aerosol containing 25% isobutane, the animals lay prostrate but recovered rapidly. In the other isobutane-containing groups, the animals were lethargic following exposure. Recovery was rapid in the group containing no isobutane. There were no visible lesions at necropsy of the animals in this series of tests.

Studies of formulations containing fluorocarbon resin.

Two exposures

There was a 60% mortality during exposure to the formulations containing 20 and 25% isobutane, whereas no mortalities occurred in any other group. In the 20 and 25% isobutane groups, anesthesia was moderate to deep and respiration was deep and rapid. In the other groups, anesthesia was light and respiration was rapid.

Following exposure to all of the formulations, the animals were immediately lethargic but were normal the following day.

Petechial hemorrhages were observed in the lungs of the animals that died. Necropsy of the surviving animals showed that punctate hemorrhages were present in the lungs of the animals exposed to formulations containing 20 and 25% isobutane. In the other groups, there were fewer punctate hemorrhages in the lung.

5. Toxicity

Id Gases
Date 03.10.2001

Ten exposures

Formulations containing 0, 15, 20 and 25% isobutane were tested. Mortality occurred only during exposure as follows:

| <u>% Isobutane</u> | <u>% mortality</u> |
|--------------------|--------------------|
| 0 | 40 |
| 15 | 0 |
| 20 | 60 |
| 25 | 100 |

Moderate anesthesia occurred in the groups exposed to formulations containing 0 and 15 % isobutane and recovery was rapid. In the group exposed to 20% isobutane, anesthesia was deep and recovery was slow.

Results of the gross necropsies are summarised as follows:

| <u>% Isobutane</u> | <u>Gross necropsy</u> | |
|--------------------|---|------------------------------------|
| | <u>Deaths</u> | <u>Survivors</u> |
| 0 | Foci of hemorrhage in lung Acute passive congestion in liver Congestion in kidney | Foci of chronic hemorrhage in lung |
| 15 | --- | Punctate hemorrhage in lung |
| 20 | Ecchymatic hemorrhage in lung | ----- |
| 25 | Diffuse congestion in lung | ----- |

Remark

This study was of formulations containing isobutane and is of limited value, since it is not possible to attribute any of the effects observed to any single component of the formulations. However, mortality was increased in those formulations containing the highest concentrations of isobutane.

Reliability

: (2) valid with restrictions

(14)

5. Toxicity

Id Gases
Date 03.10.2001

Type : LC₅₀
Species : mouse
Sex : no data
Exposure time : 2 hour(s)
Value : 680 mg/l
Method : No details given of experimental conditions
Year : 1969
GLP : no data
Test substance : Butane, not specified further
Result : Confidence limits given as 596-775.
 LC₅₀ value and limits
 determined by method of Litchfield & Wilcoxon.
Reliability : (3) invalid
 Study not performed to guidelines and some experimental
 details lacking.

(36)

Type : LC₅₀
Species : mouse
Strain : other: CF-1
Sex : male
Number of animals : 10
Vehicle : air
Exposure time : 120 minute(s)
Value : 520400 ppm
Year : 1977
GLP : no data
Test substance : Isobutane
Method : Groups of 10 male mice were exposed by inhalation to isobutane at various
 concentrations in air for 120 minutes. Oxygen was added (25% of the
 volume of isobutane) to prevent any death due to hypoxia. An LC₅₀ and
 95% fiducial limits were calculated by a **probit** method.
 No further experimental details are provided.
Result : Signs of central nervous system depression, rapid and shallow respiration,
 loss of posture, and apnea were observed.
 Mortality at the various exposure concentrations is as follows.

| <u>Concentration (%)</u> | <u>Mortality (%)</u> |
|--------------------------|----------------------|
| 36 | 0 |
| 40 | 10 |
| 50 | 30 |
| 55 | 50 |
| 60 | 90 |
| 65 | 100 |

Reliability : The 120 minute LC₅₀ was determined to be
 52.04± 3.26 %v/v (equivalent to 520,400 ppm).
 (2) valid with restrictions
 Full experimental details are not provided, nevertheless, the data are useful
 in assessing the acute inhalation toxicity of isobutane.

(9)

5. Toxicity

Id Gases
Date 03.10.2001

Type : LC₅₀
Species : mouse
Strain : CF-1
Sex : male
Exposure time : 120 minute(s)
Value : 539600 ppm
Year : 1977
GLP : no data
Test substance : mixture of isobutane, butane and propane
Method : Groups of 10 male mice were exposed by inhalation to the gas mixture at various concentrations in air for 120 minutes. Oxygen was added (25% of the volume of isobutane) to prevent any death due to hypoxia. An LC₅₀ and 95% fiducial limits were calculated by a probit method. No further experimental details are provided.

Result : Mortality was reported thus:

| <u>Concentration (% v/v)</u> | <u>Mortality (%)</u> |
|------------------------------|----------------------|
| 45 | 0 |
| 50 | 20 |
| 55 | 50 |
| 60 | 60 |
| 70 | 80 |
| 75 | 100 |

LC₅₀ determined to be 57.42 ±3.46%

The authors reported that the gas mixture exhibited less toxicity than isobutane alone, but did not report any clinical signs. The tendency for the mixture to be less toxic was attributed to the presence of propane which is less toxic than either butane or isobutane.

It was also reported that there was no significant difference between the LC₅₀ for isobutane alone and the gas mixture.

Test condition : The following gas mixture was tested:
Isobutane (31 psig) 80.4%
Butane (17 psig) 2.5%
Propane (108 psig) 17.1%

Mixture (46 psig)

(8)

5. Toxicity

Id Gases
Date 03.10.2001

Type : other: EC₅₀
Species : dog
Exposure time : 5 minute(s)
Year : 1982
GLP : no data
Test substance : Propane and Isobutane
Method : Method not described, but reference given to previous publication by authors which does include a description of the method.

Result : EC₅₀ for cardiac sensitization to adrenaline in dogs after 5 mins. exposure to propane and isobutane are given below. Values given are the EC₅₀ expressed as concentration in air (ppm) with 95% confidence limits.

| | |
|------------------|--|
| Propane | 180000 (120000-260000) [= 324,640 (216,427-468,925) mg/m ³] |
| Isobutane | 70000 (47000-1 06000) [= 166,405 (111,729-251,985) mg/m ³] |

Reliability (4) not assignable
Inadequate description of study.

(11)

Type : cardiac sensitization to epinephrine
Species : dog
Vehicle : air
Exposure time : 10 minute(s)
Year : 1948
GLP : no data
Test substance : Ethane, propane, n-Butane, **iso-Butane**
Method : Electrocardiograms, Lead II, were recorded from the unanesthetised dogs.
 Epinephrine hydrochloride solution (1 :100000) was injected i.v. at a dose of 0.01 mg/Kg over a 25 to 40 second time interval.
 After administration of the epinephrine HCl another ECG was taken.
 Each animal was subsequently permitted to breathe a mixture of hydrocarbons in varying concentrations (15 to 90%) mixed with oxygen.
 After 10 minutes' inhalation of the hydrocarbon, an ECG trace was made following administration of epinephrine HCl as described above.

Result : Sensitisation of the myocardium **occured** at the following incidence:

| <u>Hydrocarbon</u> | <u>No. of dogs sensitized/No. exposed</u> |
|--------------------|---|
| Ethane | 2/4 |
| Propane | 3/3 |
| n-Butane | 2/2 |
| iso-Butane | 2/2 |

The authors reported the results with 12 different hydrocarbons. Only those of relevance to this dossier are summarized here.

Remark This work is an experimental study carried out as part of a program to examine the usefulness of different materials as anesthetics. Although not a guideline study, it nevertheless demonstrates the potential of some hydrocarbons to sensitize the myocardium to epinephrine.

Reliability (4) not assignable

(25)

5. Toxicity

Id Gases
Date 03.10.2001

Type : Anesthetic activity
: In a cosmetic ingredient review the following information is summarized.

Isobutane

Mice

35% in air for 25 mins. fairly effective as anesthetic
41-52% in air Lethal in 2-3 minutes

Dogs

45% in air Relaxation occurs
55% in air Lethal

Isopentane

Mice

9% in air Anesthesia in 11 minutes
11% in air Anesthesia in 2 minutes

Dogs

12% in air Not anesthetic
15-17% Lethal

n-Butane

Mice

13% Light anesthesia and
excitement in 25 minutes

22%

Anesthesia in 1 minute

Dogs

20-25% Lethal

Reliability : (4) not assignable
Original data were not reviewed and the quality of the data cannot,
therefore, be verified.

(4)

5.1.3 ACUTE DERMAL TOXICITY

: Not applicable

5.1.4 ACUTE TOXICITY, OTHER ROUTES

: Not applicable

5.2.1 SKIN IRRITATION

Species

: rabbit
: In a Cosmetic ingredients review, data are presented (tabulated) on the
skin irritation potential of various cosmetics formulations.
Erythema and edema scores are provided for each of the formulations
tested on the shaved intact skin of rabbits.

15 formulations were tested containing Isobutane at concentrations ranging
from 74.25 to **89.55%**, and the Primary irritation indices for these were
similar and ranged from 1.895 to 0.52, respectively.

Results are also tabulated for six formulations containing both isobutane
and propane (approximately in the proportion of 65 parts isobutane to 12
parts propane), and for these the **PIIs** ranged from 0.38 to 0.855.

Reliability : (4) not assignable

(4)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
: The following statement is made in Grant's Toxicology of the Eye, under the heading Butane:
"Butane is an essentially nontoxic petroleum gas which causes no disturbance of the eye, even when injected into the anterior chamber experimentally in rabbits. I found it disappeared spontaneously from the eye in two to four days, causing no disturbance."
No other details are provided.

Reliability : (3) invalid
This is an unreliable piece of anecdotal information and should not be used in an evaluation of the eye irritancy potential of butane.

(18)

Species : rabbit
: The following statement is made in a Cosmetic Ingredient Review, published in 1982:

" A hair spray, containing 22% concentration of isobutane, was tested for eye irritation in five rabbits. A 0.1 ml of the undiluted product was sprayed into one eye, and after 4 sec the eye was irrigated. There was no sign of **corneal** irritation after 1 h. There was transient iritis and mild conjunctivitis after one hour, but these soon disappeared."

Reliability : (4) not assignable
This data does not relate directly to isobutane but is, nonetheless, useful supporting information.

(4)

5.3 SENSITIZATION

: Not applicable

5. Toxicity

Id Gases
Date 03.10.2001

5.4 REPEATED DOSE TOXICITY

Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 90 days
Frequency of treatment : 6 hours/day, 5 days/week
Post obs. period : None
Doses : 0, 1017 & 4489 ppm
Control group : yes, concurrent no treatment
NOAEL : 4489 ppm
Method : OECD Guide-line 413 "Subchronic Inhalation Toxicity: 90-day Study"
Year : 1986
GLP : no data
Test substance : Two mixtures were tested as follows:
n-butane/n-pentane 50/50 wt.%
isobutane/isopentane 50/50 wt.%
The mixtures were prepared by gravimetrically filling gas cylinders with 50lb. of each component and then compressing the cylinders to 250 psi. The components were 99% minimum purity.

Test condition : Inhalation exposures were conducted in Rochester-type 1 m³ stainless steel chambers.
Test atmospheres were achieved by flash evaporation of the liquid phase components as they were released from the storage cylinders.
Hydrocarbon concentrations in the chambers were monitored and adjustments made as necessary in order to achieve the desired atmospheres.

Method : 20 male and 10 female six-week old rats were exposed to each concentration, 6 hours each day for 5 days each week. Total duration of the study was 90 days.
A negative control group of 40 male and 20 female rats were exposed to filtered air under otherwise similar conditions. The rats were observed daily throughout the study, were weighed weekly and immediately prior to sacrifice. Necropsies were performed on half the male rats in each treatment group after the 20th exposure and for the remaining animals at the conclusion of the 90-day study. At necropsy, the presence of lesions and other abnormal conditions was noted and liver and kidney weights determined.
Major tissues, except for kidneys were collected and fixed, but not examined microscopically.
Kidneys were fixed and examined histologically.

Result : There were no mortalities in the study.
Possible treatment-related but NOT dose-related effects included transient hunched posture and/or lethargy and intermittent tremor. Statistically significant decreases in body weight **occured** in both sexes by weeks 3 and 4 when exposed to the n-butane/n-pentane mixture. Recovery **occured** by the end of the study for males but not for the females. There were no treatment-related gross lesions observed, nor were there any kidney or liver weight changes following exposure.

5. Toxicity

Id Gases
Date 03.10.2001

- Nephrotoxicity was observed after 20 exposures in males at both dose groups of the **butane/pentane** mixture but this had disappeared by 90 days.
A similar effect **was** seen in males after 20 exposures to 1000 ppm of the **isobutane/isopentane** mixture, but again this was not apparent in the rats exposed for 90 days.
The authors concluded that although there had been a slight nephrotoxic response in male rats after 20 exposures, this was transient and was not present after 90 days exposure.
It is concluded, therefore, that the NOAEL (concentration) is 4489 ppm.
- Remark** : The purpose of this study was to examine the possible nephrotoxic effects of **C₄** and **C₅** hydrocarbons present in gasoline. Due to the limited scope of the study, organ weight measurements were restricted to kidney and liver and histopathological examinations also restricted to the kidney.
- Reliability** : (1) valid without restriction

(5)

5.5 GENETIC TOXICITY 'IN VITRO'

- Type** : Ames test
System of testing : Salmonella typhimurium, reverse mutation assay using strains TA98, TA100, TA1535, TA1537 & TA1538.
Concentration : Concentrations ranging between 1 to 50% in air.
Metabolic activation : with and without
Result : negative
Method : other: OECD 471, modified to test gaseous substances
Year : 1980
GLP : no data
Test substance : Six gases of the following composition were tested:

Aas
n-Butane 99.7%
iso-Butane 0.3%

Bas
iso-Butane 96.3%
n-Butane 3.8%
propane 0.3%

Cas
Propane >99.9%
iso-Butane trace
n-Butane trace

Das
iso-Pentane 97.2%
n-Pentane 2.8%

Eas
n-Pentane 98.7%
cycloPentane 0.6%
cis-pentane-2 -

Fas
iso-Butane 97.4%
n-Butane 2.19%
propane 0.4%
ethane 0.01%

5. Toxicity

Id Gases
Date 03.10.2001

- Method** : Duplicate plates seeded with the respective Salmonella strains (with and without **S9** fractions) were placed in desiccators from which air was withdrawn and replaced by the gases under test. Test concentrations were 10, 20, 30, 40 and 50% in air.
The plates were exposed for 6 hours to the gas mixtures in the sealed desiccators, after which time they were removed and incubated at 37°C for an additional 40-45 hours. The number of histidine revertants were counted and recorded. Negative and positive (methylene chloride) controls were also carried out.
Rat **S9** fractions were used for metabolic activation. The authors do not specify the criteria they used for a positive response.
- Result** : The revertants per plate for each of the test material and controls is shown in the following table. Only the results from the highest non-toxic concentrations are shown.

| Material +/- activation | Conc'n | Salmonella strain | | | | |
|---------------------------------------|--------|-------------------|--------|--------|------|--------|
| | | TA1535 | TA1537 | TA1538 | TA98 | TA1 00 |
| Negative control | | | | | | |
| - activation | | 15 | 12 | 10 | 29 | 138 |
| + activation | | 16 | 18 | 30 | 38 | 155 |
| Positive control (methylene chloride) | | | | | | |
| - activation | 2 | 34 | 10 | 16 | 234 | 900 |
| + activation | 2 | 52 | 12 | 52 | 237 | 1066 |
| <u>Gas A (n-butane)</u> | | | | | | |
| - activation | 50 | 24 | 6 | 18 | 22 | 122 |
| + activation | 50 | 26 | 4 | 37 | 48 | 134 |
| <u>Gas B (isobutane)</u> | | | | | | |
| - activation | 50 | 23 | 4 | 7 | 26 | 108 |
| + activation | 50 | 10 | 4 | 16 | 26 | 98 |
| <u>Gas C (propane)</u> | | | | | | |
| - activation | 50 | 20 | 18 | 14 | 18 | 114 |
| + activation | 50 | 18 | 5 | 16 | 21 | 88 |
| <u>Gas D (isopentane)</u> | | | | | | |
| - activation | 10 | 22 | 3 | 14 | 15 | 124 |
| + activation | 10 | 10 | 6 | 16 | 22 | 124 |
| <u>Gas E (n-pentane)</u> | | | | | | |
| - activation | 10 | 25 | 1 | 8 | 26 | 138 |
| + activation | 10 | 14 | 6 | 22 | 18 | 116 |
| <u>Gas F (isobutane)</u> | | | | | | |
| - activation | 40 | 23 | 10 | 10 | 28 | 103 |
| + activation | 40 | 7 | 6 | 14 | 18 | 91 |

The positive control (methylene chloride) was mutagenic in strains **TA98** and **TA1 00** and was slightly mutagenic in **TA1535**. Neither n-butane, isobutane, nor propane were toxic or mutagenic at any of the concentrations tested.

Isopentane was toxic at concentrations of 10% and above. Further studies were carried out at 1, 2, 5 and 8% and no mutagenicity was found at these lower concentrations.

n-Pentane was toxic at concentrations of 25 and 50%.

5. Toxicity

Id Gases
Date 03.10.2001

Further studies were carried out at 1, 2, 5, 8 and 10%, and no mutagenicity was found at these non-toxic concentrations.

Gas F (97.4% Iso butane) was weakly toxic at a concentration of 50%, but was not mutagenic at concentrations of 5, 10, 20, 30 or 40%.

In conclusion, none of the hydrocarbons were mutagenic with or without metabolic activation in the Ames Salmonella assay in 5 strains exposed for 6 hours in desiccators.

Reliability : (2) valid with restrictions

(24)

5.6 GENETIC TOXICITY 'IN VIVO'

: No data

5.7 CARCINOGENICITY

: No data

5.8 TOXICITY TO REPRODUCTION

: No data

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

: No data

5.11 EXPERIENCE WITH HUMAN EXPOSURE

: During laboratory investigations of workers bottling liquefied propane and butane, most of the workers complained of respiratory symptoms (e.g., dry cough and dry throat together with gastrointestinal effects). The electrocardiographic findings in some workers indicated sinus tachycardia, extrasystole and incomplete right bundle branch block.

Lactic acid production in workers experiencing propane "poisoning" has been reported as slight.

Eight adult volunteers of both sexes were exposed to isobutane in a controlled-environment chamber to monitor their physiological responses to a series of gas concentrations ranging from 250 to 1000 ppm [=594-2377 mg/m³].

Initially, the response to exposure periods of 1 and 2 minutes, and 1, 2 and 8 hours were studied. Since there were no untoward responses, the eight volunteers were then exposed repetitively to isobutane at a concentration of 500 ppm [=1189 mg/m³] for 1, 2 or 8 hours a day, five days a week for 2 weeks. This was followed by studying the effects of exposure to 2 mixtures of isobutane and propane for 1, 2 or 8 hours a day for 2 days.

During the studies, the subjects were kept under strict medical surveillance.

No untoward subjective or physiological responses were recorded either during or after the exposures.

Special attention was placed on evaluating cardiac and respiratory effects by the use of continual ECG telemetry

5. Toxicity

Id Gases

Date 03.10.2001

and **computerised** spirometric measurements. Additionally, the following serial laboratory investigations were unaltered by the exposures: complete blood count, urinalysis, serum alkaline phosphatase, SGOT, LDH, serum bilirubin, blood sugar, serum calcium, serum phosphorus, BUN, spontaneous EEG, visual evoked responses, a battery of cognitive tests, and an ACTH stimulation test. Ikoma records 20 cases of sudden death in which propane and propylene were found in the blood, urine and cerebrospinal fluids of the victims.

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