Doc. 1

Trimethylolpropaan [redacted]

Aanvrager: N.V. Chemische Fabriek v/h Dr. A.Haagen,
Postbus 44,
Roermond

per brief Bn/wd dd. 9-10-1967.

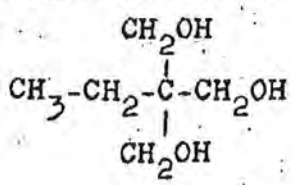
13 G4
dd. 28-2-1968

Conclusie: Afgewezen - per brief dd. 19-3-1968, G4-6
" " " 19-4-1968, G4-18

[redacted] zal Dr. Haagen verzoeken, te specificeren welke stof(fen) bedoeld is (zijn) en aan te geven welke hoeveelheid men wil toepassen. Indien aanvrager bereid is 3 mnd. tox. proeven te nemen en de vereiste tox. en migratiegegevens te verzamelen, zou overwogen kunnen worden de nader gespecificeerde stof(fen) gedurende bijv. een jaar tijdelijk toe te staan.

Brief Dr. Haagen dd. 11-4-1968:

Er wordt speciaal trimethylolpropaan bedoeld:



Brief [redacted] aan Dr. Haagen, G4-18 dd. 19-4-1968

De commissie G4 zal proberen over TMP toxiciteitsgegevens bij elkaar te zoeken uit literatuur die wellicht voor Dr. Haagen minder toegankelijk is.

17 G4
dd. 10-6-1968

Van TMP is alleen een LD/50 bekend.
[redacted] zal aanvrager mededelen, dat hulpstof alleen op gegevens volgens de "Richtlijnen" in [redacted] toegelaten kan worden.

Brief [redacted] aan Dr. Haagen, G4-36, dd. 5-6-1968

Afwijzing medegedeeld.

Doc. 2

10.2.e, tenzij anders aangegeven

19 maart 1968
84 - 6
10.1.c [redacted]
Uw aanvrage dd. 9-10-'67

N.V. CHEMISCHE FABRIEK v/h
DR. A. HAAGEN
Postbus 44,
R O E R M O N D
Ter attentie van
De W[redacted]erde Heer
DR. [redacted]

Mijne Heren,

Verschillende subcommissies van de Adviescommissie Warenwet hebben zich met Uw aanvrage bezig gehouden en mij verzocht, U op de hoogte te brengen van de stand van zaken.

1. Benzoëzuur 10.1.c [redacted]

2. Calcium-o-methoxybenzoaat:
10.1.c [redacted]

3. Zink-2-ethylhexoaat:
10.1.c [redacted]

4. Trimethylolpropaan en andere hexaantriolen:

In deze algemene vorm kan geen toelating worden verleend. Indien U specificaties kunt aangeven, voor welke triolen plaatsing op de "positieve lijst" gevraagd wordt, zou het kunnen zijn dat van deze specifieke verbindingen voldoende gegevens bekend zijn. In het algemeen verdient het echter aanbeveling indien U, eventueel in samenwerking met de verbruikende industrie van elke hulpstof uit deze reeks die U nogmaals aan wilt vragen, de gewenste toxiciteits- en migratiegegevens in Uw brief bijvoegt.

In afwachting van Uw berichten,

hoogachtend,

b.d.: [redacted]

[redacted]

Bijl.: 1.

10.2.e, tenzij anders aangegeven

Doc. 3

NV CHEMISCHE FABRIEK
v/h DR. A. HAAGEN
BILLITON - SECTOR CHEMIE

Adviescommissie Warenwet,
Nassau Zuilensteinstraat 21,
's-GRAVENHAGE.

Ref.: Bn/wd

Roermond, 11 april 1968.

Mijne Heren,

Betr.: 10.1.c [redacted]

In Uw brief G4-6 d.d. 19 maart 1968 schrijft U, dat over de toxiciteit van calcium-o-methoxybenzoaat te weinig bekend is. Wij hebben ons inmiddels met het CIVO te Zeist in verbinding gesteld en aldaar zal een onderzoek worden uitgevoerd. Zodra wij hierover een rapport hebben ontvangen, zullen wij ons wederom met U in verbinding stellen.

Onder punt 4: "Trimethylolpropaan en andere hexaantriolen" verzoekt U ons specifikaties aan te geven voor welke triolen plaatsing op de "positieve lijst" wordt gevraagd, zodat U kunt nagaan of van de bewuste specifieke verbinding voldoende gegevens bekend zijn. Wij willen ons beperken tot het 1.1.1 trimethylolpropaan:

Betreffende deze stof, die tot 10.1.c [redacted] zenden wij U hierbij literatuurgegevens over de eigenschappen.

Wij verzoeken U ons te berichten of U voldoende gegevens over 1.1.1 trimethylolpropaan ter beschikking staan om voor te stellen deze stof als 10.1.c [redacted] toe te staan. Mocht dit niet het geval zijn, dan vernemen wij dit gaarne van U.

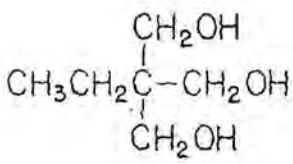
Hoogachtend,

N.V. CHEMISCHE FABRIEK
v/h Dr. A. HAAGEN
[redacted]

Bijlagen

ROERMOND (NEDERLAND)
POSTBUS 44
MOLENWEG 10
TELEFOON (04750) 5841
TELEX 58021
TELEGRAMADRES COLORI

Trimethylolpropane is a white, low-melting solid containing three primary hydroxyl groups. Also known as 1,1,1-tris(hydroxymethyl) propane, and 2-ethyl, 2-hydroxymethyl-1,3-propanediol, this aldol condensation product is represented by the following structural formula:



SPECIFICATIONS

Hydroxyl content, wt %, min	37.5
Acidity, as formic, wt %, max	0.002
Color of 10% aqueous solution, platinum-cobalt units, max	5
Freezing point, C, min	58.0
Phthalic color, Gardner, max	1
Water content as packaged, wt %, max	0.05

PHYSIOLOGICAL PROPERTIES

Trimethylolpropane is an essentially non-toxic polyol. It has a very low acute oral and dermal toxicity as evidenced by tests performed on male albino rats. The acute oral LD_{50} for the male albino rat is 14.7 grams per kilogram. The acute dermal LD_{50} of trimethylolpropane for albino rabbits is greater than 10 grams per kilogram. Patch tests performed on 200 humans indicate that trimethylolpropane is neither a primary skin irritant nor a skin sensitizer.

TYPICAL PHYSICAL PROPERTIES

A comprehensive listing of typical physical properties and constants of trimethylolpropane, based on laboratory work and reliable reference sources, is presented in the following tables and charts. Thermodynamic constants and other engineering data appear in Table 1. A white, flaked product, trimethylolpropane is hygroscopic and precautions to maintain a low moisture level should be observed. The ability to absorb moisture makes this polyol a useful humectant. Figure 1 shows this behavior at various relative humidities. Although insoluble in hydrocarbons, trimethylolpropane has varying degrees of solubility in a variety of other solvents as indicated in Table 2. Figure 2 shows the infrared spectrum of a regular production sample of trimethylolpropane after vacuum drying, required in the potassium bromide wafer technique. The low vapor pressure of this polyol, represented in Figure 3, and its high latent heat of vaporization, estimated at several temperatures in Table 3, minimize its loss from reaction vessels. Values for the density of molten trimethylolpropane at various temperatures, listed in Table 4, are useful in processing measurements.

Table 1. Typical Properties

Ash content, wt %	<0.005
Molecular weight, calculated	134.18
Boiling point C, at:	
5 mm Hg abs	160
50 mm Hg abs	210
760 mm Hg abs	295
Fire point, Cleveland open cup, F	380
Flash point, Cleveland open cup, F	355
Heat of combustion, k cal per g mole	864
Heat of fusion, cal per g	43.83
Specific heat, solid, at 30.9 C, cal per g per deg C	0.581
Melting point, deg C	58.8

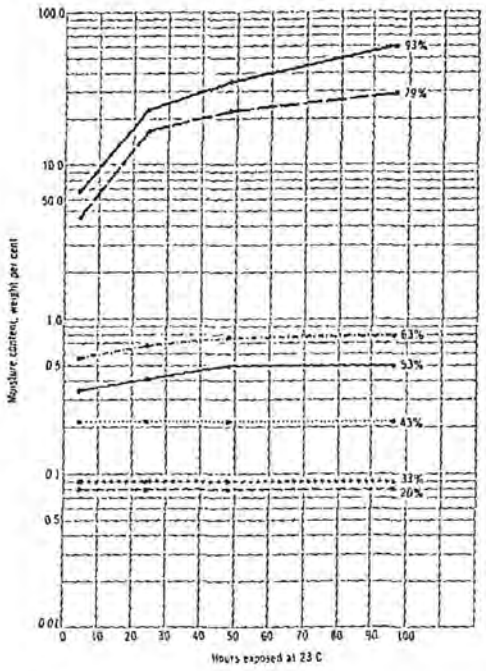
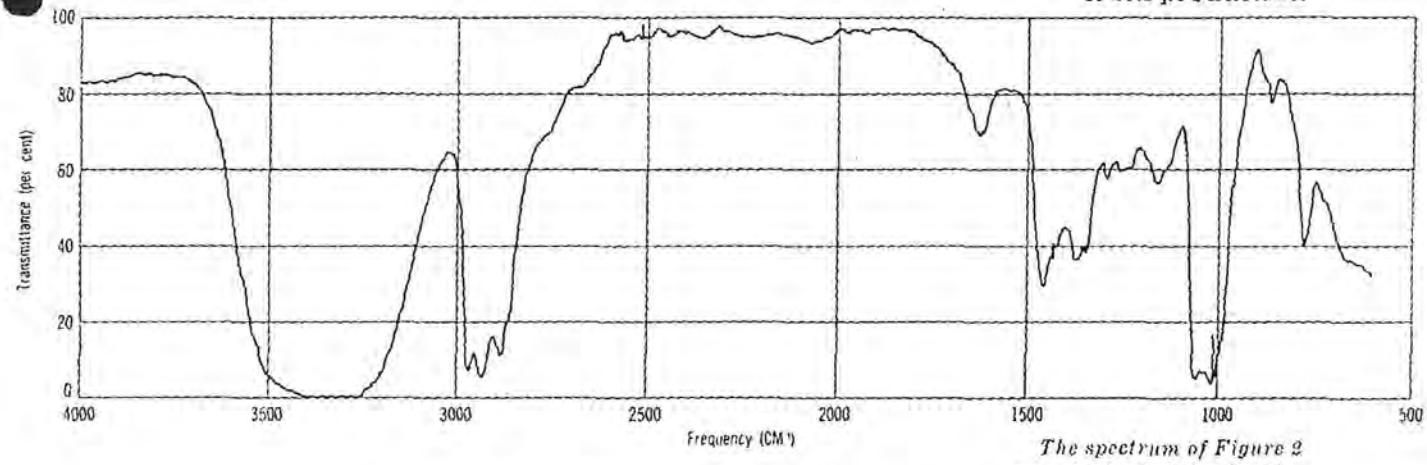


Figure 1
Moisture content of trimethylolpropane versus exposure time at various relative humidities

Figure 2
Infrared spectrum of sample of trimethylolpropane from production



The spectrum of Figure 2 was obtained with a Perkin-Elmer Model 221 Spectrophotometer equipped with prism grating interchange. Slit program was 950, gain 3.0, and scale 50 cm/cm. The wafer contained 1.6 mg dried trimethylolpropane per 500 mg potassium bromide.

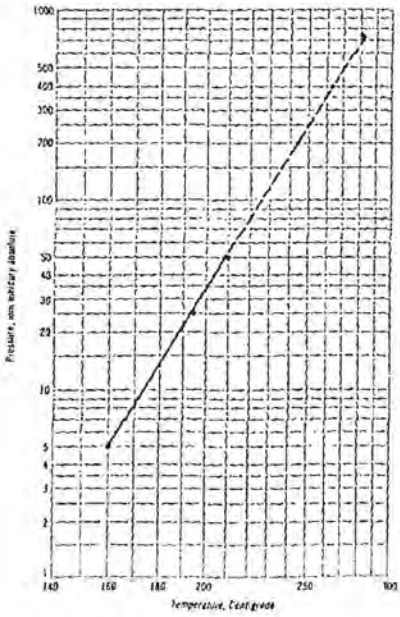


Figure 3
Vapor pressure of trimethylolpropane

In Figure 3, the three values joined by the solid line were determined experimentally. The values joined by the broken line were calculated using the Antoine vapor pressure equation, the constants of which were determined by the substitution of the laboratory-derived figures reported in Table 3. These Antoine constants are $A = 12.4716$, $B = 6341.11$, and $C = 378.6$.

CA 1060g dd. 22-4-'68
J 403/68 Tox. 9E

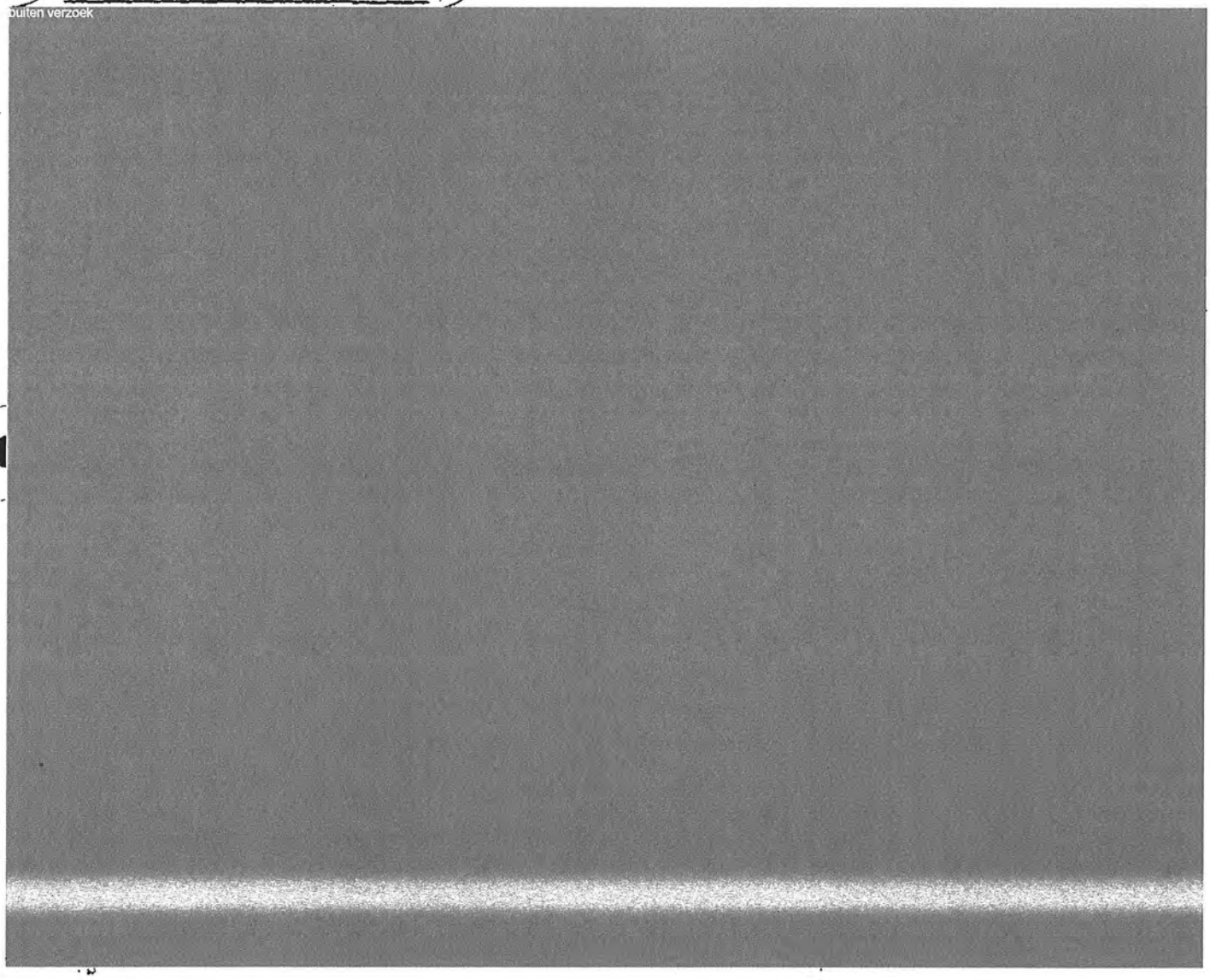
19 april 1968
G4 - 18
Antioxydant Weston 243B
Trimethylolpropaan

N.V. Chemische Fabriek v.h.
Dr. A. Haagen,
Postbus 44,
R O E R M O N D

Mijne Heren,

In antwoord op Uw brieven Bn/wd dd. 11-4-1968 moge ik het volgende opmerken:

Antioxydant Weston 243B



Trimethylolpropaan

Eigenlijk is deze aanvrage evenals de vorige onvolledig. Aangezien het hier echter een vrij bekende chemische stof betreft, waarover wellicht toxicologische gegevens bekend zijn die voor U minder toegankelijk zijn dan voor de leden van de Adviescommissie, zal voor deze hulpstof een eerste literatuur-studie gemaakt kunnen worden.

Hierbij is het zeer onwaarschijnlijk dat men ook gegevens zal kunnen vinden t.a.v. de migratie van deze hulpstof in het levensmiddel. Deze gegevens zult U uiteraard zelf moeten verschaffen, alsmede toxiciteitsgegevens indien blijkt dat deze uit de literatuur onvoldoende bekend zijn.

Het spijt mij dat ik U in beide gevallen een vrij negatief antwoord op Uw brieven moet geven, doch U zult begrijpen dat het de taak van de aanvrager is voor de nodige gegevens te zorgen. Ik hoop U t.z.t. nog over trimethylolpropaan te kunnen berichten en verblijf,

hoogachtend,

[redacted]

b.c.: [redacted]

CA 14941 dd. 6-6-'68
J 551/68 Tox. VE

5 juni 1968
G4 - 36
Trimethylolpropaan

N.V. Chemische Fabriek
v.h. Dr. A. Haagen,
Postbus 44,
R O E R M O N D

Mijne Heren,

Terugkomend op Uw brief Bn/wd dd. 11-4-1968 en op onze brief G4-18 dd. 19-4-1968 moet ik U mededelen dat geen toxiciteitsgegevens in de literatuur te vinden waren met betrekking tot trimethylolpropaan. Indien U er prijs op stelt, deze stof als [redacted] 10.1.c op de "positieve lijst" vermeld te krijgen, dient U bij een eventuele hernieuwde aanvrage gegevens t.a.v. toxiciteit en migratie in te sluiten.

Bij het bepalen, welke gegevens noodzakelijk zijn kunt U zich laten leiden door de "Richtlijnen", zoals deze in de Nederlandse Staatscourant Nr. 87 dd. 6 mei jl. zijn gepubliceerd.

Weliswaar wordt deze hulpstof op verschillende plaatsen door de FDA toegestaan, maar zover de commissie kon nagaan, steeds als component die met andere componenten reageert zo dat de aanwezigheid in het eindprodukt te verwaarlozen is.

Het spijt mij U geen positiever bericht te kunnen zenden.

Hoogachtend,

[redacted]

b.c.: [redacted]

G4-723/MM
11826/(17)1 dd. 30.5.1973

13 Juni 1973
TMP In 10.1.c

De Hoogedelgestrenge Heer
[redacted]
Secretaris Adviescommissie
Warenwet
Dokter Reijerstraat 10
LEIDSCHENDAM

Zeer geachte [redacted]

Hiermede deel ik U mede, dat de via U ontvangen aanvrage van de Zweedse Firma Perstorp A.B. dd. 11.4.1973 om toelating van 1,1,1-tris (hydroxymethyl)propaan door GO G4 op 5 juni j.l. is behandeld.

De commissie heeft, na onderzoek van de ter beschikking gestelde gegevens besloten, U gunstig te adviseren over de toelating van deze hulpstof [redacted] 10.1.c (bijlage 8, Hoofdstuk I onder 8.2.d.), mits de migratie ervan in levensmiddelen (resp. simulanten) bepaald volgens de methoden van onderzoek, aangegeven in Hoofdstuk X niet meer bedraagt dan 30 mg per dag.

De commissie zou nog graag nader geïnformeerd worden of een smelttraject van 58-60° C nodig is voor een produkt met een zuiverheid van minimaal 99%, maar de toelating behoeft niet op het antwoord op deze vraag te wachten.

Met de meeste hoogachting,

[redacted]
Secretaris Commissie "G4"
(In zijn afwezigheid ondertekend door [redacted]
Secr.)

cc. Drs. [redacted]

Doc. 8

Trimethylpropaan in PVC
1,1,1-tris(hydroxymethyl)propaan

Aanvrager: Perstorp A.B.
Zweden

80 G4 d.d. 5-6-1973
Van [redacted], ref. 11826/(17)1 dd. 30-5-1973 het verzoek van Perstorp A.B. dd. 11-4-1973 om toelating van 1,1,1-tris(hydroxymethyl)propaan als [redacted]
Uit de bijgevoegde toxiciteits-studie (CIVO rapport Nr. R3037 dd. nov. 1969) volgt een NTEL van 0,1% waaruit met F=100 een PADI x 60 berekend wordt van 30 mg per dag.
Perstorp zal gevraagd worden naar de mogelijkheid het smelttraject van 58-60°C (zuiverheid 99%) te verkleinen.

Conclusie: G4 zal gunstig adviseren over toelating van 1,1,1-tris(hydroxymethyl)propaan [redacted] (bijlage 8, Hoofdstuk I onder 8.2.d). (Doorgegeven aan [redacted] met G4-723/MW dd. 13-6-1973).

Doc. 9

108e "G4" 16-11- 1976

glyoxaal - des.
hexamethyleen tetramine - fad
emulgatoren - f. ad

3. papierlijst

a. glyoxaal, gebruikt voor het modificeren van eiwitten en het in water onoplosbaar maken van zetmeel.
Het met glyoxaal gemodificeerde zetmeel (oorspronkelijk nr. 22) is afgewezen als voedingszetmeel.
Alleen LD/50 is onderzocht: 0,2 - 2,0 mg/kg rat (30 % in water).

Conclusie G4: onvoldoende tox. gegevens, dus afwijzen of in de migratielijst opnemen: niet aantoonbaar.
Gewenste tox. gegevens: 90-dagen en Ames-test.

De Milde zal trachten na te gaan of glyoxaal als zodanig analytisch bepaald kan worden of dat men glyoxaal als formaldehyde bepaalt.

b. hexamethyleentetramine

FAO/WHO-voorstel voor max. dagelijkse dosis: 9 mg/mens. Het Visbesluit staat 0,1 % in sommige visconserven toe; het CEE-ontwerp noemt 0,05 % = 500 mg per kg geconserveerde vis als maximum.

Conclusie G4: toelaatbaar, doch aangezien hexamethyleentetramine analytisch als formaldehyde wordt bepaald, zou de specifieke migratie afzonderlijk of tezamen met HCOH in totaal op 1 gesteld moeten worden.

c. ~~chattigum~~, wederom door de papierindustrie aangevraagd. Geen tox. gegevens beschikbaar en stof niet toegelaten door FAO/WHO.

Conclusie G4: niet toelaatbaar; 90-dagen-voederproef met ratten gewenst.

d. N,N'-bis(2-hydroxyethyl)glycine: onzekerheid t.a.v. de formule en geen tox. gegevens bekend.

Conclusie G4: niet toelaatbaar; 90-dagen-voederproef vereist en precisering van de structuurformule.

e. 1,1,1-tris(hydroxymethyl)ethaan: op grond van de analogie met de propaan-verbinding (PADI x 60 = 30) wel toelaatbaar, doch met een extra veiligheidsfactor PADI x 60 verlagen tot 3.
Indien deze migratiewaarde voor de industrie te laag is, zou een eenvoudige voederproef, waarin beide stoffen met elkaar worden vergeleken, voldoende kunnen zijn. Speciaal dient gelet te worden op de afwijkingen in de proefdieren gevonden met het wél onderzochte 1,1,1-tris(hydroxymethyl)propaan.

Doc. 10

109e Bijeenkomst Commissie "G4" dd. 1 maart 1977 te Bilthoven

Verslag 108 G4

blz. 2, sub e: 1,1,1-tris(hydroxymethyl)propaan is door CIVO in een 90-dagen studie voor Perstorp en Bayer onderzocht: Rapport # 3057 dd. nov. 1969; RIV-overzicht dd. augustus 1973, behandeld in 80 G4. Beslissing medegedeeld met brief G4-723 dd. 13-06-75; produkt overzicht aanwezig.

10.2.e, tenzij anders aangegeven

Doc. 12

advlescommissie warenwet

Kaapmanstraat 1
2280 BC Rijswijk (ZH)
Correspondentie uitsluitend:
Postbus 5811, 2280 HV Rijswijk (ZH)
Telefoon: 070-949505

18.AUG.1982 • 010480
I624/82 CBS

AAN:
- de leden, adviseurs en deskundigen van de Subcommissie Methoden van Chemisch-Analytisch onderzoek
- de leden, adviseurs en deskundigen van de Subcommissie Verpakkingen
- de drie vertegenwoordigers der departementen

datum : 16 augustus 1982
onderwerp : Verpakkingen- en gebruiksartikelenbesluit (Warenwet)
ons kenmerk: 13355/(17)1

De Werkgroep Analytische Methoden Verpakkingen heeft een drietal nieuwe ontwerp-methoden ter opneming in deel B (Methoden van Onderzoek) van de Bijlage bij de Uitvoeringsbeschikking van de artikelen 2 en 5 van het Verpakkingen- en gebruiksartikelenbesluit (Warenwet) opgesteld (zie bijlage), te weten

./.

- 4.3.28 Migratie van 2-fenylindool
- 4.3.29 Migratie van 1,1,1-tris (hydroxymethyl)propaan
- 4.3.30 Migratie van secundaire aromatische aminen

Uw eventuele opmerkingen met betrekking tot deze ontwerp-methoden zou ik gaarne vóór 11 september 1982 van U ontvangen.

De secretaris,

[redacted]

Bijlage bij brief Adviescie Warenwet aan Sektie Verpakkingen dd 16-8-82

10.2.6 tenzij anders aangegeven

Doc. 12

4.3.29 Migratie van 1,1,1-tris(hydroxymethyl)propaan

4.3.29.1 Migratie in waterige simulanten

a. beginsel

Het materiaal wordt met 3 % azijnzuur* in kontakt gebracht. Na afloop van de bewaarperiode wordt de vloeistof gescheiden van het voorwerp en onder verminderde druk verdampt. De in het residu aanwezige hoeveelheid 1,1,1-tris(hydroxymethyl)-propaan wordt na acetylering kwantitatief bepaald met behulp van gaschromatografie.

b. toestellen

- laboratoriumglaswerk
- apparatuur voor gaschromatografie

c. reagentia

- acetonitril p.a.
- azijnzuuranhydride p.a.
- interne standaardoplossing: oplossing van diethylftalaat: 35 mg/ml in aceton
- standaardoplossing van 1,1,1-tris(hydroxymethyl)propaan: 10 mg/ml in aceton

d. ijklijn

Breng van de standaardoplossing respectievelijk 0; 1,0; 2,0; 4,0 en 6,0 ml in een konische kolf van 50 ml. Damp het oplosmiddel af. Voeg 2 ml azijnzuuranhydride en twee druppels acetonitril toe. Plaats een terugvloeikoeler op de kolf en kook het mengsel gedurende circa 20 min. Voeg vervolgens 0,5 ml interne standaardoplossing toe en 40 ml acetonitril. Breng van de oplossingen telkens 1 µl op de gaschromatografische kolom. Meet in het chromatogram de hoogten van de pieken van de geacetyleerde 1,1,1-tris(hydroxymethyl)propaan en van de interne standaard en bereken de piekhoogteverhouding. Zet de verkregen waarden grafisch uit tegen de in bewerking genomen hoeveelheden 1,1,1-tris(hydroxymethyl)propaan.

---

* Er wordt aangenomen, dat de migratie van 1,1,1-tris(hydroxymethyl)-propaan in water en in 15 % ethanol gelijk is aan die in 3 % azijnzuur.

e. gaschromatografie

De gaschromatografische bepaling kan bijvoorbeeld onder de volgende omstandigheden worden uitgevoerd:

- gaschromatograaf met vlamionisatiedetektor
- kolom: glas, lengte 2 m, inw. diam. 3 mm
- kolomvulling: 3 % OV1 + 2 % OV17 op Chromosorb W AW, 60-80 mesh
- kolomtemperatuur: 180 °C
- gassnelheden: stikstof: 35 ml/min; waterstof: 60 ml/min; lucht: 300 ml/min

f. uitvoering van de migratieproef

Breng zoveel materiaal als overeenkomt met tenminste 6 dm^2 (stel b dm^2) in een passend bekerglas.* Voeg, indien mogelijk, per 6 dm^2 100 ml 3 % azijnzuuroplossing toe. Dek het bekerglas met een horlogeglas af en plaats het gedurende de voorgeschreven tijd in een ruimte bij de voorgeschreven temperatuur (zie 1.3). Schenk de vloeistof na afloop van de bewaarperiode af in een konische kolf van 500 ml en damp met behulp van een roterende verdamper onder verminderde druk tot een volume van ca. 3 ml in. Breng het residu vervolgens met aceton over in een konische kolf van 50 ml en handel verder als onder d is beschreven.

g. bepaling van 1,1,1-tris(hydroxymethyl)propaan

Breng 1 µl van de verkregen oplossing op de gaschromatografie-kolom. Meet in het chromatogram de hoogte van de pieken van de geacetyleerde 1,1,1-tris(hydroxymethyl)propaan en van de interne standaard. Bereken de piekhoogteverhouding en leid uit de ijkgrafiek de hoeveelheid 1,1,1-tris(hydroxymethyl)-propaan af.

i. berekening

Stel dat de hoeveelheid a mg is. Bereken hieruit de specifieke migratie Ms van 1,1,1-tris(hydroxymethyl)propaan met de formule:

$$Ms = \frac{a}{b}\ mg/dm^2$$

* Kleine houders, sluitingen en gedekte en gelaagde materialen worden op de onder 4.4.1 aangegeven wijze met de simulant in kontakt gebracht.

4.3.29.2 Migratie in vet

a. beginsel

Het materiaal wordt met de vetsimulant in kontakt gebracht. Na afloop van de bewaarperiode wordt het vet van het voorwerp gescheiden. De 1,1,1-tris(hydroxymethyl)propaan wordt met water uit het vet geïsoleerd. De oplossing wordt drooggedampt en de hoeveelheid 1,1,1-tris(hydroxymethyl)propaan in het residu wordt vervolgens, na acetylering, kwantitatief bepaald met behulp van gaschromatografie.

b. toestellen

- laboratorium glaswerk
- apparatuur voor gaschromatografie

c. reagentia

- vetsimulant: een synthetisch triglyceridenmengsel, gemerkt Fettsimulans HB 307 (zie 1.3.1)
- n-pentaan p.a.
- acetonitril p.a.
- aceton p.a.
- azijnzuuranhydride p.a.
- interne standaardoplossing: oplossing van diethylftalaat: 35 mg/ml in aceton
- standaardoplossing van 1,1,1-tris(hydroxymethyl)propaan: 10 mg/ ml in aceton

d. ijklijn

Breng in vijf scheitrechters van 500 ml telkens 50 g vet. Voeg respectievelijk 0; 1,0; 2,0; 4,0 en 6,0 ml van de standaard-oplossing en 100 ml pentaan toe en meng. Schud de oplossingen vervolgens vier maal met telkens 25 ml water. Verzamel de waterextracten in rondbodemkolven van 500 ml en damp met behulp van een roterende verdamper onder verminderde druk in tot een volume van ca 3 ml. Breng het residu in elke kolf vervolgens met aceton over in een konische kolf van 50 ml en handel verder als onder 4.3.29.1.d is beschreven.

e. uitvoering van de migratieproef

Breng zoveel materiaal als overeenkomt met tenminste 6 dm^2 (stel b dm^2) in een passend bekerglas.* Voeg, indien mogelijk, per 6 dm^2 50 g voorverwarmd vet toe en sluit het bekerglas af met een horlogeglas. Plaats het bekerglas gedurende de voorgeschreven tijd in een ruimte bij de voorgeschreven temperatuur (zie 1.3). Schenk na afloop van de bewaarperiode het vet af in een scheitrechter van 500 ml en handel verder als onder d is beschreven.

f. bepaling van 1,1,1-tris(hydroxymethyl)propaan

Breng 1 µl van de verkregen oplossing op de gaschromatografiekolom. Meet in het chromatogram de hoogte van de pieken van de geacetyleerde 1,1,1-tris(hydroxymethyl)propaan en van de interne standaard. Bereken de piekhoogteverhouding en leid uit de ijkgrafiek de hoeveelheid 1,1,1-tris(hydroxymethyl)propaan af.

g. berekening

Stel dat de hoeveelheid a mg is. Bereken hieruit de specifieke migratie Ms van 1,1,1-tris(hydroxymethyl)propaan met de formule:

$$Ms = \frac{a}{b}\ mg/dm^2$$

---

* Kleine houders, sluitingen en gedekte en gelaagde materialen worden op de onder 4.4.1 aangegeven wijze met de simulant in kontakt gebracht. Zorg er voor, dat de verhouding vloeistof : kontaktoppervlak ten hoogste 50 g vet per 6 dm^2 bedraagt, bijvoorbeeld door het toevoegen van glasparels.

Solubility of trimethylolpropane in various solvents

Solvent	Solubility at	
	room temperature	50 °C
Acetone	Soluble	Soluble
Aliphatic hydrocarbons	Insoluble	Insoluble
Aromatic hydrocarbons	Insoluble	Insoluble
Carbon tetrachloride	Insoluble	Insoluble
Chlorinated hydrocarbons	Insoluble	Insoluble
Cyclohexanone	Partly soluble	Soluble
Diethyl ether	Insoluble	-
Diethylene glycol dimethyl ether	Insoluble	Soluble
Dimethyl sulfoxide	Soluble	Soluble
Dioxane	Partly soluble	Soluble
Ethanol	Completely soluble	Completely soluble
Ethyl acetate	Partly soluble	Partly soluble
Glycerine	Completely soluble	Completely soluble
Mesityl oxide	Partly soluble	Soluble
Methyl ethyl ketone	Partly soluble	Soluble
Methylene chloride	Insoluble	-
Methyl Cellosolve	Partly soluble	Soluble
Water	Completely soluble	Completely soluble

Investigation of the migration of trimethylolpropane from [redacted]

1. Type of packaging material

A [redacted] bottle intended for use for packaging of carbonated beverages. The bottle consists of an upper conical part and a lower bulb, both made from [redacted] The bulb is supported by an outer cylindric thick-walled paper casing.

Conical part

Inner surface area:	80 cm^2
Thickness:	76 mg/cm^2

Bulb

Inner surface area:	300 cm^2
Thickness:	41 mg/cm^2
Total volume	450 cm^2
Total [redacted]	18 g

[redacted] type: [redacted] bottle compound.

Stabilizer: Ca/Zn, non-toxic type. Level 2,5 phr. .

Trimethylolpropane [redacted]

2. Preparation of samples; method of extraction

The tests have been performed according to the BGA regulations, described in "Kunststoffe im Lebensmittelverkehr", Fragebogen B, point 14, page XVI i. See also B Gesundh Bl. 4 (1961) Nr 12, page 189.

The bottles have been cut to larger pieces and any adhering dust has been removed by the use of a non-dusting cloth. The material has then been cut into 2 x 2 cm pieces and weighed into 10 g portions. These have been conditioned at 20°C and 65 % relative humidity for 24 hours in a desiccator containing a bowl with saturated sodium nitrite solution. Each sample has been transferred into a 500 ml round-bottomed flask. In the flask, the sample has been contacted with 250 ml extraction liquid at 35°C 10 days. The following extraction liquids have been used:

1. Distilled water (pH ca 7)
2. 10 % aqueous ethanol
3. 3 % aqueous acetic acid
4. Coconut oil

From each of the extracts 1, 2 and 3, 25 ml samples have been withdrawn and slowly evaporated under atmospheric pressure to approximately 1,5 g. Comparative experiments have shown that no TMP is lost during these conditions.

1) Only Ca and Zn salts approved by BGA have been used.

Extract 4 was heated in à different manner. The oil sample was extracted with 2 x 25 ml distilled water. (Comparative test runs were made, which showed that essentially all of 1 ppm TMP added to a 25 ml oil sample was extracted during these conditions). The sum of water extracts was then evaporated to ca 1,5 g.

The evaporated extracts were then analysed for TMP by a vapour phase chromatography method, using the following conditions:

Instrument:	Varian 1740, 1-mV recorder
Column:	Stainless steel, length 100 cm, diameter 1/8"
Packing material:	3 % OV-1 (silicone rubber) on Chromosorb GHP 80/100 mesh
Carrier gas:	Nitrogen, 18 psi
Column temperature:	155°C
Injection volume:	1 μl
Injection temperature:	200°C
Detector:	Flame ionization
Detector temperature:	250°C
Attenuation:	4×10^{-11}

Two test-runs were made. In one series, the thicker material was extracted (76 mg/cm^2); in the the second series, the thinner material (41 mg/cm^2). Calibration was made in the range 0,25-10 ppm, calculated on extract before evaporation. The calibration solutions were prepared from TMP and distilled water. Peak height was used as a measure of concentration. An example of a chromatogram is shown in Picture 1 together with calibration chromatograms from the lower end of the concentration range.

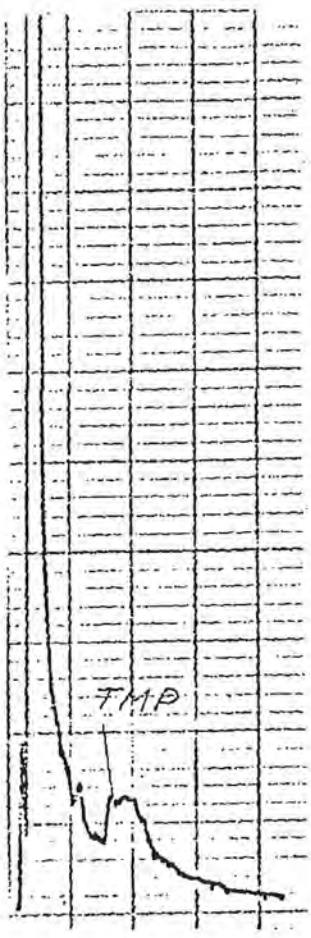
Results

These are shown in the following table.

Extraction liquid	Concentration in liquid, ppm		Amount extracted, mg per 600 cm^2 exposed packing material[2)]
	thick material	thin material	
Distilled water	< 0,5	< 0,5	< 0,2
10 % ethanol	5[1)]	< 0,5	2[1)]
3 % acetic acid	< 0,5	< 0,5	< 0,2
Coconut oil	< 0,5	< 0,5	< 0,2

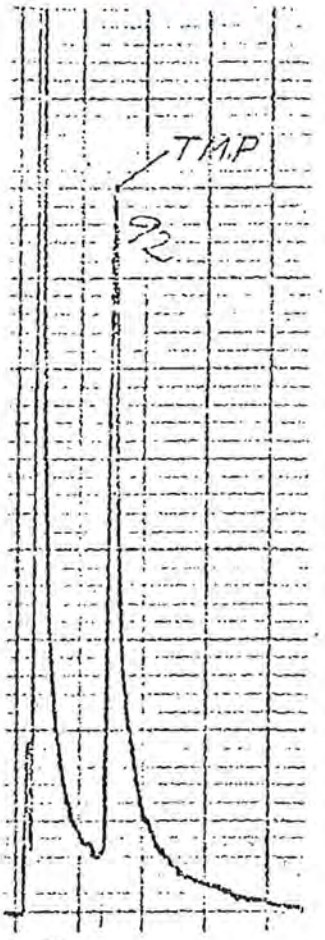
1) In this chromatogram, a large number of peaks appeared in the TMP area. Probably, contamination of this sample has taken place.

2) Calculated from the proportions of thick and thin materials in the packaging item.



0,25 ppm

0,50 ppm



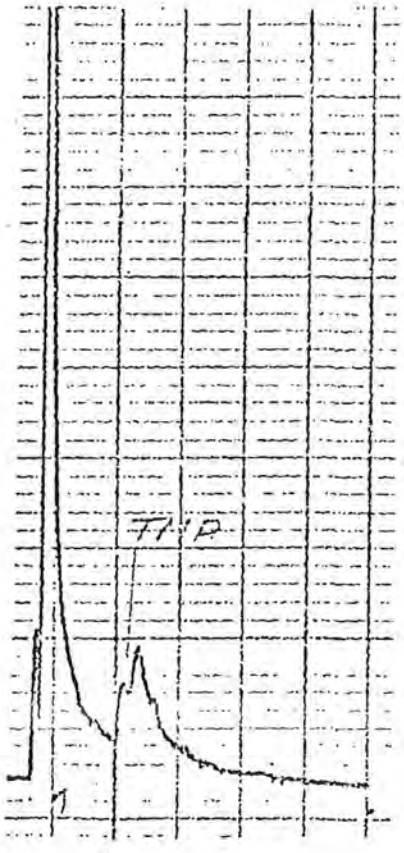
1,0 ppm

Above:

Chromatograms on calibration solutions of TMP in distilled water.

To the right:

Chromatogram on distilled water extract.



Picture 1

Appendix 3

10.2.e, tenzij anders aangegeven

Doc. 12.3

CENTRAAL INSTITUUT VOOR VOEDINGSONDERZOEK

Utrechtseweg 48
Zeist

CENTRAL INSTITUTE FOR NUTRITION AND FOOD RESEARCH
INSTITUT CENTRAL DE LA NUTRITION ET DE L'ALIMENTATION
ZENTRALINSTITUT FÜR ERNÄHRUNGSFORSCHUNG

RAPPORT NR. R 3037

Subchronic (90-day) toxicity study with trimethylolpropane (TMP 99) in albino rats

Authors: [redacted]

Approved by: [redacted]

Date: november 1969

Number of copies: 8

Summary

1. The toxicity of trimethylolpropane was examined in a sub-chronic (90-day) toxicity study with albino rats. The test material was fed at levels of 0, 0.03, 0.1, 0.3 and 1.0 % in stock diet to groups of ten male and ten female weanling rats each.

Observations were made of general appearance and behaviour, growth, food intake and efficiency, haematological factors and urine composition. Examinations were made on the blood serum for enzyme activities viz.SGOT, SGP, SAP and for total serum protein and albumin.

At week 14 all rats were killed and examined grossly. Several organs were weighed and extensive histopathological examination was carried out.

2. General appearance and behaviour, gain in body weight, food intake and efficiency, blood serum enzyme activities, serum protein content and urine composition were not noticeably affected by the feeding of the test compound at any dietary level.

3. Haemoglobin content was decreased in females at 1.0 %. Packed cell volume and red blood cell counts were decreased in females at 0.3 and 1.0 %. Blood smears contained normoblasts and white blood cell fragments in both sexes at 1.0 % and normoblasts in females at 0.3 %.

4. The relative weight of the spleen was increased in both sexes and liver, kidney and ovary weights were increased only in females at the highest feeding level. Pituitary weight was increased in males at 1.0 %. At 0.3 % all relative organ weights were within the normal range.

5. Gross examination at autopsy revealed enlarged dark spleens at the 1.0 % level in both sexes.

At the microscopic examination pathological changes were seen in spleen (increased number of cells in the red pulp) and liver (Kupffer cells laden with pigment, sinusoids containing normoblasts and too many small lymphocytes) of males and females only at the highest feeding level.

6. It was concluded that the no-toxic-effect-level of trimethylolpropane (TMP 99) is 0.1 % in the diet of rats for three months.

Subchronic (90-day) toxicity study with trimethylolpropane (TMP 99) in albino rats

1. INTRODUCTION

The toxicity of trimethylolpropane was examined in a subchronic (90-day) toxicity study with albino rats as experimental animals. The substance to be examined was fed to groups of 10 male and 10 female rats at levels of 0, 0.03, 0.1, 0.3 and 1.0 % in stock diet.

Growth, symptomatology, food consumption, haematology, biochemical blood observations, urine analyses, organ weights and gross and microscopic pathology were used as criteria to disclose possible harmful effects.

2. MATERIAL AND METHODS

A sample of trimethylolpropane, coded TMP 99, was received from the principal on 20th December 1968. An infrared spectrum of the test material is shown in figure 1.

Fifty male and 50 female weanling rats from the C.I.V.O.-colony (Wistar - derived) were divided according to body weight over five groups of ten males and ten females each, and fed on stock diet with trimethylolpropane added at levels of 0, 0.03, 0.1, 0.3 and 1.0 %.

The percentage composition of the stock diet was as follows:

yellow maize	26.6	brewers' yeast	3
whole wheat	36	grass meal	3
soybean oil meal	10	soybean oil	3
meat scraps	4	vitamin preparations	3.4
fish meal	8	trace mineralized salt	0.5
dried whey	2	calcium phosphate	0.5

The test compound was thoroughly mixed into the diet by means of a mechanical blender (type Lödige, Paderborn, Western Germany). The diets were freshly prepared once a fortnight and stored at room temperature.

The animals were housed in screen bottom cages (five to a cage) in a room of constant temperature at ca 24 °C. Food and tap water were constantly available.

Individual body weights were recorded weekly. The food intake of each group was determined during the first four weeks and during weeks 11 and 12.

Haematological data consisting of haemoglobin content, packed cell volume, red blood cell counts and total and differential white blood cell counts were recored in weeks 4 and 12.

Determinations of serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), serum alkaline phosphatase (SAP), total serum protein, albumin and albumin-globulin ratio were carried out at the end of the experiment.

Urine examinations, including appearance, pH, glucose, albumin, occult blood and ketones were conducted upon pooled urine samples of ten males and ten females of each group in week 13.

In week 14 all rats were killed by decapitation and examined macroscopically for pathological changes.

The following organs were weighed: heart, kidney, liver, spleen, brain, testicle or ovary, thymus, pituitary, thyroid and adrenal. Samples of these organs and of a wide range of other organs were fixed in a 4 % neutralized formaldehyde solution.

Detailed microscopic examination was performed on all male and female rats of the highest dose group and of all control rats. Haematoxylin-eosin stained paraffin sections of the organs weighed and also of the following organs were examined: lung, salivary glands (sublingual, submaxillary and parotid gland), gastro intestinal tract (six levels), trachea, skeletal muscle, aorta, exorbital lacrimal gland, axillary and mesenteric lymph nodes, pancreas, skin, urinary bladder, sternum with marrow, prostate, epididymis, coagulating gland, seminal vesicle, preputial gland, uterus, spinal cord and femoral nerve.

Microscopic examination of rats at lower dosages (0.03, 0.1 and 0.3 %) was restricted to liver and spleen.

3. RESULTS

3.1. General condition, growth and food consumption

During the course of the experiment no deaths occurred and no abnormalities of condition or behaviour were observed.

Table 1 shows average body weights. There were no significant differences in body weight between the various groups, although at the three highest feeding levels body weights of males were consistently lower than in controls.

Average food consumption and food effiency figures are given in table 2.

Food consumption and food efficiency figures did not show consistent differences between groups.

3.2. Haematology

Average haematological data recorded at weeks 4 and 12 are given in table 3.

At 1 % haemoglobin contents of females were slightly lower than in the controls. The difference was only significant at week 4. Red blood cell counts and packed cell volume of females were decreased at the two highest dose levels at week 12. The blood smears showed normoblasts and white blood cell fragments in males and females at 1 % in week 4. In week 12 normoblasts were observed in males at 1 % and in females at 0.3 % and 1.0 %. In females at 1.0 % they occurred in considerable numbers. The differential counts did not reveal consistent differences between groups.

3.3. Biochemical blood observations

Average biochemical values at the end of the experimental period are shown in table 4.

There were no distinct or significant differences between the experimental groups and the controls.

3.4. Urine analyses

The results of the urine analyses are presented in table 5.

There was no alteration of the urine which could be attributed to the feeding of trimethylolpropane.

3.5. Organ weights

The average relative organ weights (expressed in g/100 g body weight) are given in table 6.

Spleen weights were significantly increased at 1.0 % in both sexes. The average relative weights of kidneys, liver and ovary were significantly, statistically, increased in females at 1.0 %. In males pituitary weight was increased at 1.0 %.

A few organ weights (brain weight at 0.1 % and ovary weight at 0.03 % in females), which differed significantly from the controls, were considered incidental findings because they did not suggest a relationship with the dietary level of the test material.

3.6. Pathology

3.6.1. Gross examination

Moderately enlarged, dark spleens were seen in males and females of the highest dose group. Other gross changes attributable to the test substance were not seen.

Occasional lesions found at autopsy such as early signs of murine pneumonia and unilateral hydronephrosis, are regulary seen in the strain of rats used. They may therefore not be ascribed to the ingestion of the test compound.

3.6.2. Microscopic examination

At microscopic examination (see table 7) pathological changes related to trimethylolpropane were found in spleen and liver.

Increased numbers of small lymphocytes, normoblasts and megakaryocytes were encountered in the red pulp of the spleen in males and females of the highest dose group. The white pulp of the spleen was unremarkable.

Normoblasts and an increased number of small lymphocytes were also present in the sinusoids of the livers of males and females at the 1 % level. Slightly enlarged Kupffer cells containing yellowish brown pigment were seen in two females of the highest dose group.

At lower levels, spleen and liver were histologically indistinguishable from those of the controls.

The other microscopic changes occurred only in a single animal or were about equally distributed between test and control animals. Therefore, they are not regarded of toxicological importance.

From gross and microscopic examination it appears, that 1 % trimethylolpropane induced pathological changes in the spleen and the liver. At lower levels no treatment related morphological changes were detected.

4. DISCUSSION AND CONCLUSION

The feeding of trimethylolpropane to young rats at various dietary levels up to 1.0 % for three months resulted in distinct ill effects only at the highest feeding level. The abnormalities consisted of slightly decreased haemoglobin levels and red blood cell counts and the presence of normoblasts and white blood cell fragments, increased relative weights of kidneys, liver and spleen and microscopical changes in liver and spleen.

At the 0.3 % level, the only significant difference with the controls consisted of decreased packed cell volume and red cell counts and increased occurrence of normoblasts in the blood of females. These phenomena did not occur at lower levels.

On the basis of the present results, the no-toxic-effect-level of trimethylolpropane (TMP 99) is placed at 0.1 % in the diet of rats for three months, which is equivalent with 50 mg/kg body weight/day.

C.I.V.O. &x MdV
18th November 1959

Table 1. Average body weights during a feeding period of 13 weeks

group nr.	% trimethyl-olpropane in the diet	average body weight (in g) at end of week 0	2	4	6	8	10	12	13
		groups of 10 males							
2417	0	53.4	117.9	185.9	235.5	272.0	297.7	321.9	329.1
2418	0.03	53.0	116.8	192.4	237.3	269.0	292.7	314.8	327.1
2419	0.1	53.1	111.3	183.0	226.8	257.3	280.9	303.9	314.4
2420	0.3	53.0	114.6	187.2	230.1	261.5	283.6	306.8	318.3
2421	1.0	53.3	110.1	183.4	228.5	260.2	281.6	305.0	316.4
		groups of 10 females							
2417	0	51.2	96.2	133.0	149.4	168.8	178.7	190.0	192.7
2418	0.03	51.4	97.1	134.6	152.0	169.2	177.5	190.8	195.6
2419	0.1	51.1	98.6	138.2	157.2	174.8	185.6	199.3	203.9
2420	0.3	50.6	100.5	137.5	157.9	171.3	180.4	192.5	197.0
2421	1.0	51.1	97.0	136.8	156.7	171.6	182.6	191.5	200.3

Table 2. Average food consumption and food efficiency (gain/food)

group nr.	% TMP 99 in the diet	average food consumption (g/animal/day) in week 1	2	3	4	11	12	food efficiency gain/food during week 1-4
		groups of 10 males						
2417	0	8.6	12.9	15.0	17.3	18.3	18.1	0.34
2418	0.03	8.4	12.7	15.1	15.7	17.7	17.8	0.37
2419	0.1	7.9	12.0	14.2	16.3	17.1	17.2	0.35
2420	0.3	8.5	12.9	15.0	16.6	17.3	17.0	0.35
2421	1.0	7.6	12.0	14.4	17.0	18.1	18.2	0.35
		groups of 10 females						
2417	0	7.3	10.5	11.4	12.5	12.6	12.0	0.27
2418	0.03	7.6	10.7	11.5	12.7	12.8	12.3	0.27
2419	0.1	7.6	10.8	11.8	12.6	13.8	13.0	0.28
2420	0.3	7.3	11.0	11.8	12.7	12.1	12.7	0.28
2421	1.0	7.2	10.6	12.0	13.4	13.4	13.1	0.27

Table 3. Haematological data of male and female rats recorded at weeks 4 and 12

group nr.	% TMP 99 in the diet	Hb g/100 ml	packed cell volume %	R.B.C.[1] x 10^{-6}/ mm^3	W.B.C.[2] x 10^{-3}/ mm^3	differential count % lymph	neutr	mono	eos
				groups of 10 males at week 4					
2417	0	15.0	46.8	7.1	16.4	86.8	12.3	0.2	0.7
2420	0.3	15.2	47.7	7.2	18.0	85.4	13.5	0.3	0.8
2421	1.0	14.5	46.9	7.2	17.4	86.7	12.0	0.3	1.0
				groups of 10 females at week 4					
2417	0	16.5	49.9	7.8	16.0	86.9	10.8	0.9	1.4
2420	0.3	16.1	48.5	7.3	17.6	88.3	9.9	0.7	1.1
2421	1.0	15.9*	49.2	7.4	19.1	88.8	8.7	0.8	1.7
				groups of 10 males at week 12					
2417	0	15.3	46.8	8.4	17.4	85.3	11.9	0.0	2.8
2418	0.03	15.5	47.2	8.1	15.9	87.0	11.0	0.0	2.0
2419	0.1	15.7	49.1**	8.1	18.5	88.0	10.1	0.0	1.9
2420	0.3	15.3	47.0	7.9	17.1	86.8	10.6	0.2	2.4
2421	1.0	15.5	47.6	8.1	19.6	86.1	11.8	0.1	2.0
				groups of 10 females at week 12					
2417	0	16.5	48.3	8.6	14.8	89.7	8.8	0.0	1.5
2418	0.03	16.2	47.6	8.5	14.2	87.3	9.8	0.1	2.8
2419	0.1	15.8	47.4	8.4	14.3	89.8	7.0	0.0	3.2
2420	0.3	15.8	46.7*	8.1*	14.9	89.2	8.6	0.1	2.1
2421	1.0	15.7	47.0	7.6**	17.8	86.2	11.1	0.0	2.7

[1]) red blood cells

[2]) white blood cells

significantly different from the controls, according to the test of Wilcoxon

*P < 0.05

*P < 0.01

Table 4. Average biochemical blood values recorded terminally

Group nr.	% TMP 99 in the diet	SGOT I m U	SGPT I m U	SAP B-L units	serum protein		
					total g %	albumin g %	albumin / globulin
		groups of 10 males					
2417	0	144	17.4	6.1	6.3	4.4	2.2
2418	0.03	151	18.7	6.2	6.1	4.3	2.4
2419	0.1	143	17.9	6.5	6.0	4.4	2.6
2420	0.3	148	17.2	5.8	6.4	4.3	2.1
2421	1.0	130	17.5	4.7	6.6	4.3	1.9
		groups of 10 females					
2417	0	152	16.8	4.4	6.2	5.3	5.7
2418	0.03	163	17.8	4.3	6.4	4.9	3.3
2419	0.1	172	17.2	3.9	6.4	4.9	3.3
2420	0.3	161	15.9	4.9	6.2	4.9	3.6
2421	1.0	146	16.1	3.9	6.5	4.7	2.7

Table 5. Results of urine analyses recorded at week 13

Group nr.	% TMP 99 in the diet	appearance	pH	sugar	protein	occult blood	acetone
							males
2417	0	yellow	6	-	±	-	-
2418	0.03	yellow	6	-	±	-	-
2419	0.1	yellow	6	-	±	-	-
2420	0.3	yellow	6	-	±	+	-
2421	1.0	yellow	6	-	±	-	-
							females
2417	0	yellow	6	-	±	-	-
2418	0.03	yellow	6	-	±	-	-
2419	0.1	yellow	6	-	±	-	-
2420	0.3	yellow	6	-	±	-	-
2421	1.0	yellow	6-7	-	±	-	-

Grading system: - = negative
± = minimal
+ = slight
++ = moderate
+++ = high

Table 6 . Body weights (in g), relative organ weights (in g/100 g body weight) and their standard deviations of groups of 10 male and 10 female rats after 13 weeks

group nr.	% trimethylol-propane in the diet	body weight	heart	kidney	liver	spleen	brain	testicle/ ovary	thymus	pituitary	thyroid	adrenal
					males							
2417	0	329 (10)	0.355 (0.014)	0.65 (0.02)	3.48 (0.08)	0.182 (0.006)	0.53 (0.02)	0.85 (0.03)	0.111 (0.008)	0.0028 (0.0001)	0.0065 (0.0005)	0.0129 (0.0005)
2418	0.03	327 (8)	0.350 (0.006)	0.64 (0.01)	3.41 (0.07)	0.178 (0.008)	0.54 (0.02)	0.85 (0.02)	0.101 (0.006)	0.0028 (0.0002)	0.0064 (0.0003)	0.0124 (0.0008)
2419	0.1	314 (9)	0.338 (0.009)	0.64 (0.02)	3.37 (0.09)	0.176 (0.006)	0.56 (0.02)	0.91 (0.02)	0.108 (0.005)	0.0027 (0.0002)	0.0057 (0.0003)	0.0139 (0.0009)
2420	0.3	318 (8)	0.347 (0.007)	0.66 (0.03)	3.41 (0.08)	0.186 (0.007)	0.55 (0.01)	0.87 (0.03)	0.107 (0.007)	0.0028 (0.0001)	0.0061 (0.0004)	0.0134 (0.0012)
2421	1.0	316 (8)	0.358 (0.009)	0.67 (0.01)	3.84 (0.17)	0.238** (0.013)	0.57 (0.02)	0.87 (0.05)	0.109 (0.005)	0.0032* (0.0001)	0.0064 (0.0004)	0.0148 (0.0011)
					females							
2417	0	193 (3)	0.386 (0.014)	0.63 (0.01)	3.14 (0.10)	0.208 (0.011)	0.87 (0.02)	0.028 (0.001)	0.149 (0.010)	0.0052 (0.0002)	0.0079 (0.0003)	0.0236 (0.0017)
2418	0.03	196 (6)	0.384 (0.009)	0.65 (0.02)	3.22 (0.13)	0.211 (0.007)	0.84 (0.02)	0.033* (0.001)	0.144 (0.008)	0.0050 (0.0004)	0.0087 (0.0005)	0.0212 (0.0016)
2419	0.1	204 (7)	0.371 (0.010)	0.66 (0.01)	3.24 (0.11)	0.215 (0.010)	0.81* (0.02)	0.031 (0.001)	0.147 (0.013)	0.0049 (0.0002)	0.0074 (0.0006)	0.0242 (0.0018)
2420	0.3	197 (8)	0.383 (0.007)	0.65 (0.01)	3.32 (0.12)	0.230 (0.006)	0.84 (0.03)	0.030 (0.001)	0.146 (0.008)	0.0049 (0.0004)	0.0083 (0.0005)	0.0257 (0.0012)
2421	1.0	200 (7)	0.405 (0.007)	0.69* (0.02)	3.55* (0.12)	0.289*** (0.009)	0.86 (0.03)	0.032* (0.001)	0.145 (0.010)	0.0053 (0.0003)	0.0077 (0.0004)	0.0233 (0.0009)

* $0.01 < p < 0.05$
** $0.001 \leq p < 0.01$
*** $p < 0.001$

Under each mean its standard deviation (in brackets) is given.

Table 7. Histopathology[1]) and the number of animals showing the observed abnormalities in the different groups

Abnormalities	males					females				
	2417 0 %	2418 0.03%	2419 0.1 %	2420 0.3 %	2421 1.0%	2417 0 %	2418 0.03%	2419 0.1%	2420 0.3%	2421 1.0%
Number of animals examined	10	10	10	10	10	10	10	10	10	10
SPLEEN										
1. INCREASED NUMBER OF SMALL LYMPHOCYTES, NORMOBLASTS AND MEGAKARYOCYTES IN THE RED PULP	0	0	0	0	10	0	0	0	0	8
LIVER										
1. ENLARGED KUPFFER CELLS CONTAINING YELLOWISH-BROWN PIGMENT GRANULES	0	0	0	0	0	0	0	0	0	2
2. SMALL LYMPHOCYTES AND NORMOBLASTS IN SINUSOIDS										
a. a very slight number	0	0	0	0	3	0	0	0	0	3
b. a slight number	0	0	0	0	1	0	0	0	0	1
3. A few small foci of reticulo-endothelial cells, occasionally accompanied by some necrotic parenchymal cells	4	3	3	2	5	3	3	6	6	3
4. Infiltrates of eosinophils, lymphocytes and plasma cells in the periportal area	0	1	1	1	2	1	2	3	2	0
KIDNEY										
1. Proteinaceous droplets within the cytoplasm of tubular epithelial cells:										
a. a few cells with droplets	4	-*	-	-	5	0	-	-	-	0
b. a moderate number of cells with droplets	0	-	-	-	2	0	-	-	-	0
2. Nephrotic tubules:										
a. a few	1	-	-	-	1	0	-	-	-	1
b. several	0	-	-	-	0	0	-	-	-	0
3. Focal interstitial nephritis	1	-	-	-	1	0	-	-	-	1
4. Cystic tubules	0	-	-	-	2	0	-	-	-	0
5. Unilateral hydronephrosis	1	-	-	-	0	0	-	-	-	0
6. Calcareous deposits in the intercortico medullary layer:										
a. a few deposits	0	-	-	-	0	5	-	-	-	4
b. a moderate number of deposits	0	-	-	-	0	1	-	-	-	0
LUNG										
1. Peribronchial, peribronchiolar and perivascular "cuffs" of lymphocytes	10	-	-	-	10	10	-	-	-	10
2. Focal interstitial pneumonitis	1	-	-	-	1	0	-	-	-	1
3. Calcareous deposits in an arterial wall	0	-	-	-	1	0	-	-	-	0
TRACHEA										
1. Peritracheal "cuffs" of lymphocytes	2	-	-	-	0	0	-	-	-	0

Table 7. Continued

Abnormalities	males					females				
	2417	2418	2419	2420	2421	2417	2418	2419	2420	2421
	0 %	0.03%	0.1 %	0.3 %	1.0%	0 %	0.03%	0.1%	0.3%	1.0%
THYROID										
1. Activated appearance seen as small follicles lined by high cuboidal epithelium										
a. a few activated follicles	4	-	-	-	4	4	-	-	-	1
b. a moderate number of activated follicles	4	-	-	-	1	1	-	-	-	0
GLANDULAR STOMACH										
1. Focus of epithelium-like cells surrounded by a few connective tissue fibres	0	-	-	-	1	0	-	-	-	0
COLON										
1. Parasite	1	-	-	-	0	0	-	-	-	0
URINARY BLADDER										
1. Proteinaceous plug	4	-	-	-	1	0	-	-	-	0
2. Parasite (Trichosomoides crassicauda)	2	-	-	-	2	3	-	-	-	2
PROSTATE										
1. Prostatitis	2	-	-	-	3					
TESTIS										
1. Unilateral atrophy	0	-	-	-	1					
ADRENAL										
1. Some foci of round cells in the cortex	0	-	-	-	1	0	-	-	-	1
HEART										
1. Slight focal myocarditis	1	-	-	-	0	0	-	-	-	0
PITUITARY										
1. Colloid cyst	3	-	-	-	0	0	-	-	-	0
PANCREAS										
1. Transformation of acinar cells into duct-like structures	1	-	-	-	0	0	-	-	-	0
SUBLINGUAL SALIVARY GLAND										
1, Hyperplasia of ductular epithelium cells	0	-	-	-	0	0	-	-	-	1

1) Treatment related histopathological changes are written in capitals
*) Not examined
Remark: The organs examined histologically, which are not mentioned in this table did not show pathological changes at all

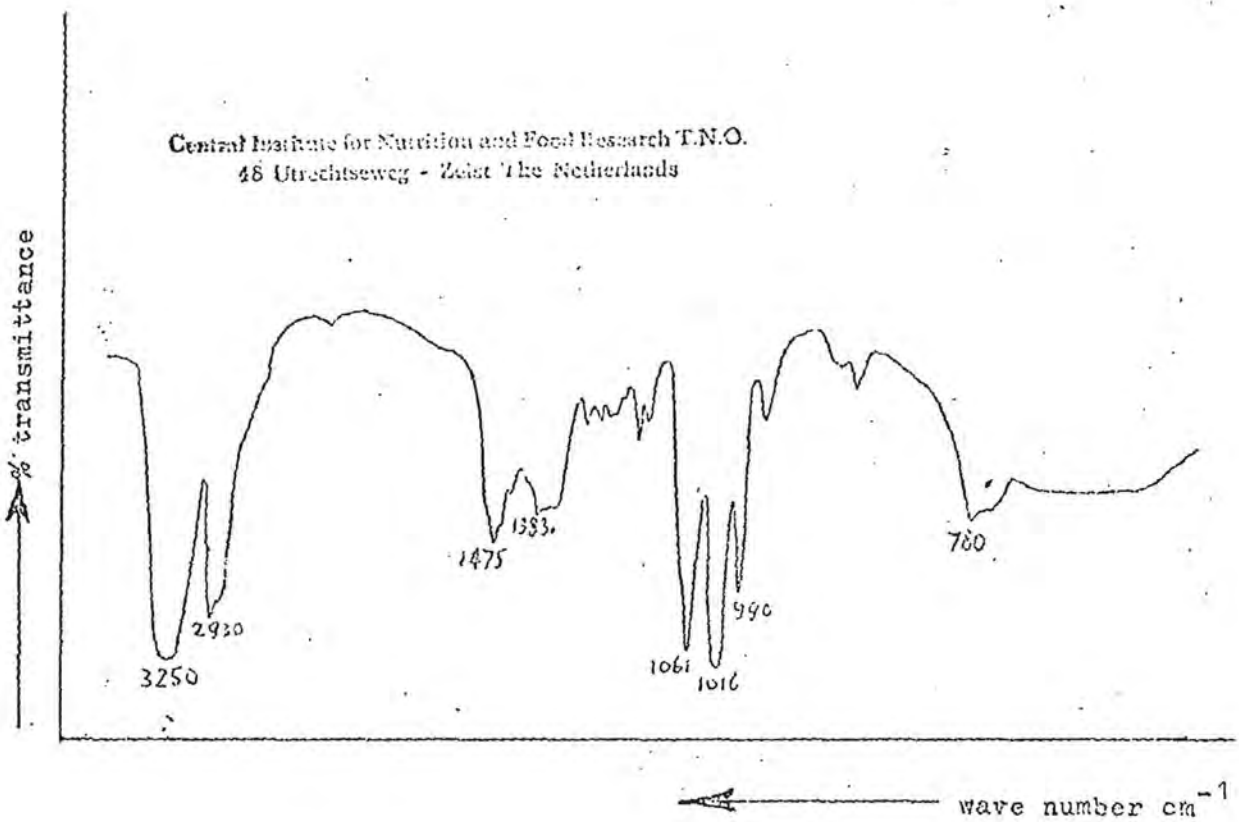


fig. 1. Infrared spectrum of "trimethylolpropane"
Perstorp AB (code TMP 99)

Phase: KBr pellet

Perstorp Polyols

Doc. 13

Chemicals Limited
P O Box 26 Mr. B.J.R. Mayes
Grimsby
South Humberside
DN27BDP
England

Our date, reference and direct dial
1989-07-03 Rkl/Saa
Your date and reference

Re: TMP approval

Dear [redacted]

Please find enclosed the study requested, which was actually done by CIVO-TNO in the Netherlands. As you may note from page 5, the no-toxic-effect level was placed at 50 mg/kg bodyweight/ day, with only a slight effect at the threefold level.

Please also find enclosed the following excerpt from a previous Council of Europe list, which places the acceptable daily intake (ADI) value at 30 mg/day equivalent to 0.5 mg/kg body weight/ per day.

We also enclose the responding letter from the Dutch authority as well as the EEC draft from 1985 also placing the ADI value at this level.

Consequently, the SCF must have applied a safety factor of 500 rather then 100. Do you have access to the corresponding SCF information (SCF 17th series, 1986) or could you advise us, how to get it? In addition, we would like to know your opinion on the practical significence of a TDI value of 0,1 mg/kg body weight for TMP.

Yours sincerly

[redacted]

Enclosure

Perstorp AB
S-284 80 PERSTORP SWEDEN
Telegram perstorpab
Telephone (Int.) +46 435 380 00
Telex 72000
Telefax (Int.) +46 435 350 19
Skandinaviska Enskilda Banken Malmö
Account No. 5662 10 000 14

Perstorp AB Sweden. 284000 Perstorp.

ontv. June 1973

Doc. 13.1

77.476

ammended Aug. 73

Application for the use of Trimethylolpropane in Food Packaging Materials

1. Applicant

Name and address are given in a covering letter.

2. Date of application

April 11, 1973.

3.1.[1] Physical and chemical data

3.1.2. Identification of the component

3.1.2.1.1. Chemical name:

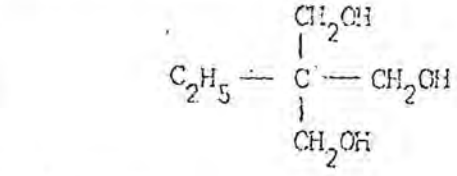
1,1,1 - trimethylolpropane, abbreviated trimethylolpropane

Synonyms:

1,1,1 - tris(hydroxymethyl)propane
2,2 - bis(hydroxymethyl)butanol-1

3.1.2.1.2. Numerical and structural formula:

$C_6H_{14}O_3$



3.1.2.1.3. Purity of substance:

Minimum 99 %.

Impurities:

[redacted]

3.1.3. Properties of the component

3.1.3.1. Relevant physical properties:

Melting point	58-60°C
Boiling point	160°C/5 mm Hg

Solubility: see appendix 1.

1) Numbers are used according to "General Guidelines for Requesting Approval of New Components in Food Packaging Materials".

3.1.3.2. Relevant chemical properties:

Very high over-all stability, especially against heat (decomposition rate less than 0,2 % per minute at 294°C in the presence of air). The high stability is partly due to the absence of hydrogen in β-position to the hydroxyls. This eliminates the point of attack for many breakdown mechanisms.

The chemical reactivity is the one normally associated with the presence of primary hydroxyl groups.

3.1.3.3. Possible decomposition products that might occur in the component during the manufacture, processing, application or use of the packaging material:
No such decomposition products are probable to occur.

3.1.3.4. Information on the persistency of the component under environmental conditions and on its fate after the packaging material or food utensil has been submitted to waste treatments:

No specific information is available. However, from our experience in trimethylolpropane production we know that the substance is biodegradable in a waste-water treatment plant of the activated sludge type.

3.2. Application of the component

3.2.1. Type of packaging material or food utensil in which the component will be used:

Trimethylolpropane is intended for use in [redacted], especially [redacted], used as food packaging materials. Examples of applications are [redacted]

3.2.2. Indication of the function of the component in the end product:

Trimethylolpropane is intended for use [redacted] as are approved for use in food packaging materials come into question.

It is well known that [redacted]. The probable mechanism is the following:

[redacted]

3.2.3. Indication of the percentage of the component to be incorporated in the packaging material or food utensil:

The maximum required [redacted]

3.3. Mobility of the component

3.3.1. An investigation of the migration of trimethylolpropane from [redacted] is shown in detail in appendix 2.

3.3.2. A suitable analytical method is described in appendix 2.

3.4. Data concerning use in other countries

No such data are available at present.

3.5. Information showing the innocuity of the component in its intended use

A subchronic (90-day) toxicity study with trimethylolpropane in albino rats have been carried out by the Central Institute for Nutrition Research (CIVO) TNO, Zeist. This investigation is shown in appendix 3.

4. Disappearing components

Trimethylolpropane is very thermally stable and will not undergo decomposition during the manufacture of the packaging material or utensil.

C.S/rm/288
Doc. 14

SCM CHEMICALS LIMITED
PO BOX 26
GRIMSBY
SOUTH HUMBERSIDE
DN37 8DP

TELEPHONE 0469 571000
TELEX 52595
FAX No. 0469 571234

Our ref. BJRM/JAW
Your ref.

25th September 1989

[redacted]
Directorate General III/B/2,
Commission des Communautes Europeenn,
200 Rue de la Loi,
B-1049 Bruxelles,
Belgium.

Dear [redacted]

We are in the process of establishing that our 'TiONA' grades of titanium dioxide pigment meet the requirements of FDA, USA. The components of these grades are titanium dioxide, with a surface treatment of aluminium compounds, silicon compounds and an [redacted] 10.1.c : 1,1,1-Tri-Methylol Propane (TMP).

All of these materials are already FDA listed as GRAS for food contact applications, except TMP, and we are therefore both examining the extraction of TMP from [redacted] 10.1.c l plastics and also seeking data on its toxicity.

Following the issue of 'Plastics Materials for Packaging (III/3141/89 Rev.1)', the 'First Report of the Scientific Committee for Food on Certain Additives Used in the Manufacture of Plastic Materials Intended to come into Contact with Foodstuffs' and the 'Consolidated Revised Report of the Scientific Committee for Food on Certain Monomers used in the manufacture of Plastic Materials Intended to come into Contact with Foodstuffs', I contacted Perstorp Polyols in Sweden regarding the Toxicity Study on TMP cited in the latter publication. They have now kindly supplied a copy of the Report, but have themselves queried the limit values/safety factors used.

I have attached a copy of their letter. Can you please comment on their questions.

Thank you.

Yours sincerely,

[redacted]
Technical Services Manager

Registered in England No. 162303
Registered Office. Stallingborough, Grimsby DN40 2PR

DIRECTION GÉNÉRALE
DU MARCHÉ INTÉRIEUR
ET DES AFFAIRES INDUSTRIELLES

III/B/2

N° télécopieur RP3 5ème étage:
téléphone: (02) 235.17.35

Doc. 15

gebracht 4-10-89

PAR TELECOPIEUR

No: 003130/742971

DESTINATAIRE: [redacted]

ADRESSE: RIVM
Postbus 1
NL 3720: BILTHOVEN

DE LA PART DE: [redacted]
DG III

OBJET: Renseignements sur l'avis du SCF

POUR ATTRIBUTION [ ]

POUR ACCORD [ ]

NOMBRE DE PAGES: 3

DATE: 3. X. 1989

OBJET: Renseignements sur l'avis du SCF

Adresse provisoire.
Rue de la Loi 200
B-1049 Bruxelles

Téléphone.
Ligne directe: 235...
Standard: 235 11 11

Telex:
COMEU B 21877

Adresse télégraphique:
COMEUR Bruxelles

Doc. 15.1

[redacted]

could you please answer to the question. I have no objection to give this information in this particular case.

Thanks

[redacted]

3. x. 89

Doc. 16

rivm
research for
man and environment

RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEUHYGIENE
NATIONAL INSTITUTE OF PUBLIC HEALTH AND ENVIRONMENTAL PROTECTION

550/89 TOX vH/mvr

Bilthoven, 25-10-1989

[redacted]

Directorate General III/B/2
Commission of the European Communities
200, Rue de la Loi
B-1049 BRUSSELS
Belgium

[redacted]

Referring to your message by telefax concerning the compound trimethylolpropane I let you know that:

- Indeed the no-effect level for this compound in a 90-day oral rat study amounts to 0.1 % in the diet equivalent to 50 mg/kg b.w. (CIVO report, 1969).
- Trimethylolpropane is on list 2 (monomers) with a TDI of 0.1 mg/kg b.w..
- A safety factor of 500 instead of 100 is used for the calculation of the TDI.
- I cannot find (in old minutes of the Working Group on Packaging Materials) the reason for the usw of a safety factor 500, but I guess it's the absence of mutagenicity data.

As I cannot give answers to all questions raised by 10.2.g [redacted], I send this letter in first instance to you. Perhaps you can complete these comments?

Yours sincerely,

[redacted]

Director Toxicology

Antonie van Leeuwenhoeklaan 9, P.O. Box 1, 3720 BA BILTHOVEN, The Netherlands
Telephone: ..(31)30-749111, Telex: 47215 rivm nl, Telefax: ..(31)30-742971

ANNEX. 17

CS/PM/323

Brussels, 15 December 1989
LR/sb
M24

III/B/2

Mr J.B.R. Mayes
SCM Chemicals Ltd
P.O. Box 26
Grimsby
GB-South Humberside
DN37 8DB

Dear Mr Mayes,

re: 1,1,1 Trimethylopropane
(Your letter BJR//JAW of 25 September 1989)

I received from Dr [redacted] the attached letter which answers the first question of Mr Perstorp's letter. As regards the practical significance of TDI value of 0,1 mg/kg bw for TMP, please read pages 11 and 12 of the attached documentation. Practically, in your case, a specific limit of migration for TMP could be fixed according to the general rule indicated in the mentioned document at 0.1 x 60 = 6 ppm in food or food simulants. However, the final decision on this compound will be taken after consultation of governmental experts.

Yours sincerely,

Encl. Extract of [redacted]
III/3141/89-En (rev 1)

Annex 1
Doc 18

SCM CHEMICALS LIMITED

PO BOX 26
GRIMSBY
SOUTH HUMBERSIDE
DN37 8DP

TELEPHONE 0469 571000
TELEX 52595
FAX No. 0469 571234

Our ref. BJRM/JAW
Your ref.

10 January 1990

[redacted]
Directorate General III/B/2,
Commission des Communates European,
200 Rue de la Loi,
B-1049 Bruxelles,
Belgium.

Dear [redacted]

Re. 1,1,1 Trimethylolpropane

Thank you for your letter of December 15th with the Extract from III/3141/-EN rev 1.

You also refer to a letter from Dr. [redacted] which was not included. Is it possible for us to see a copy of this letter please.

Yours sincerely,

[redacted]

Technical Services Manager

Registered in England No. 162303
Registered Office: Stallingborough, Grimsby DN40 2PR

10.2.e, tenzij anders aangegeven

Doc. 19

Brussels, 22 January 1990
LR/sb

III/B/2

[redacted]
Rijksinstituut voor de
Volkesgezondheid
Postbus 1
NL-3720 BA Bilthoven

Dear [redacted],

re: 1,1,1 Trimethylopropane.

I have just received a letter from SCM Chemicals Ltd, South Humberside (see Annex 1), in which [redacted] asks me to obtain a copy of your letter (addressed to me) on the above subject. Unfortunately I am unable to find your letter.

Could you please send a copy of that letter to [redacted] on my behalf.

I hope you can help me.

Many thanks,

Yours sincerely,

10.2.g [redacted]

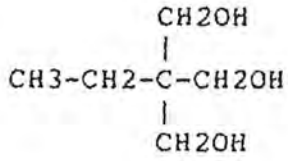
Trimethylolpropane [77-99-6] - wip.

1.1.1 1,1,1-trimethylolpropane

1.1.2 1,1,1-tris(hydroxymethyl)propane
2-ethyl, 2-hydroxymethyl-1,3-propanediol
2,2-bis(hydroxyethyl)-butanol-1 1

1.1.3 [77-99-6]

1.2.1 C6H1403



1

1.3.1 purity: > 99%

1.3.2
/3 impurities: [redacted] 10.1.c

1, 2

1.4 GC with flame ionization detector 1

2.1.1 Used as an [redacted] 10.1.c

1

Used in [redacted] 10.1.c 2

3.1 58.8 2
58-60 1

3.2 295 C at 101325 Pa 2

3.3 70 C d. 1,0889 2

3.4 666 Pa at 160 C
6666 Pa at 210 C 1, 2

3.6 soluble

3.7 soluble in alcohols, ketones, DMSO, methylcellulose;
slight soluble in ethylacetate 1, 2

3.9 355 OC

4.1.1 rat oral LD50 14.7 g/kg (no protocol) 2

4.1.3 rabbit, dermal LD50 > 10 g/kg (no protocol) 2

4.2.1 3 MONTHS ORAL RAT
5 groups of 10 m and 10 f rats (b.w. 50.6-53.4 g)
Dose: 0; 0.03; 0.1; 0.3 and 1.0% in diet
Obs : Behaviour, appearance, b.w., food cons
Hematol : Hb, Ht, Ery, Leu, Diff d 28, d 84

Biochem : SGOT, SGPT, SAP, serum, protein d 90
Urine : Appearance, pH, gluc, proteins, occult blood, acetone d 90
Organ w : 10 organs
Microscopy : of +- 30 organs and tissues of all rats in 0; 1,0% groups, and of liver and spleen of all rats in 0.3, 0.1 and 0.01% groups
Results: 1%: Hb of f at 4 wks and Er of f at 12 weeks was decreased. Blood smears of f and m contained normoblasts and white blood cell fragments. Rel. spleen weight of f + m was signif. increased Rel. pituitary wt of m was signif increased, macroscopy revealed enlayed dark spleens at m and f.
Histology revealed changes in spleen (increased no. of cells in red pulp) and liver (kupfer-cells laden with pigment; sinusoids containing normoblasts and too many small lumphocytes) at m and f
0.3%: At 12 weeks: decreased Ht and Er of f. Blood smears of f contained normoblasts
0.1%: At 12 weeks: increased Ht of m. Slightly decreased brain wt of f
0.03%: Slightly increased ovary wt of f
No effect level: 0.1% 1

5.1.1 96 hr LC50
Fish: Alburnus alburnus 10 C: > 10.000 mg/l
Nitocra spinipes 10 C: 5.250 mg/l 4

HUMANS

Dermal: 'Patch' test at 200 people
No primary irrit and sensibilization (no details) 2

Refs.:

1. Unpublished data of Perstop AB Zweden
Application for the use of Trimethylolpropane in food packaging materials
Received June 1973

2. Unpublished data of N.V. Chemische Fabriek v/h Dr. A. Haagen d.d. 11-4-1968

3. Unpublished Civo report, (private documentation) Nr. R. 3037 [redacted]
Subchronic (90-day) toxicity study with trimethylolpropane (TMP-99) in albino rats. Nov. 1969

4. Linden, E.
The acute toxicity of 78 chemicals and pesticide formulations against two brackish water organisms, the bleak (Alburnus alburnus) and the harpacticoid Nitocra spinipes
Chemosphere Nos 11/12 pp. 842-851 (1979)

10.2.e. tenzij anders aangegeven

1,1,1-TRIMETHYLYLOLPROPANE

Manufacturer

Perstop AB Zweden.

Use

10.1.c [redacted]

(1)

Dosage

Maximum required 10.1.c [redacted] %

(1)

Physical-chemical data

Chemical name

1,1,1-trimethylolpropane (1)

Synonyms

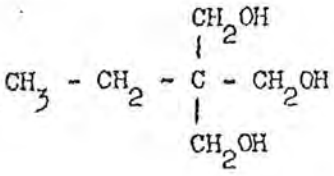
1,1,1-tris-(hydroxymethyl)-propane.

2-ethyl-2-hydroxymethyl-1,3-propanediol.

2,2-bis-(hydroxymethyl)-butanol-1 Trade name : TMP 99

(1)

Structural formula



$C_6H_{14}O_3$

(1)

Physical-chemical data

Appeareance	:	white solid
Mol.wt.	:	134.18.
M.p.	:	58-60°C .
B.p.	:	160°C (5mm Hg).
Flashpt.(open cup)	:	355°C

Solubility : solvent	room temp	50°C
acetone	soluble	soluble
aliphatic hydrocarbons	insoluble	insoluble
aromatic hydrocarbons	insoluble	insoluble
carbon tetrachloride	insoluble	insoluble
chlorinated hydrocarbons	insoluble	insoluble
cyclohexanone	partly soluble	soluble
diethylether	insoluble	-
diethyleneglycoldimethylether	insoluble	soluble
dimethylsulfoxide	soluble	soluble
dioxane	partly soluble	soluble
ethanol	completely soluble	completely soluble
ethylacetate	partly soluble	partly soluble
glycerine	completely soluble	completely soluble
mestyloxide	partly soluble	soluble
methylethyl ketone	partly soluble	soluble
methylene chloride	insoluble	-
methylcellosolue	partly soluble	soluble
water	completely soluble	completely soluble

stability: very high - over-all stability, especially against heat. (1)

Purity

Minimum 99%.

Impurities: 10.1.c [redacted] (1)

Quantitative determinations

Gaschromatography with flame ionization detector (1)

Migration

Extraction of 10.1.c [redacted] (10g of 2x2cm pieces) with 250 ml of resp. distilled H_2O (pH $\pm$ 7), 10% aqueous ethanol, 3% aqueous acetic acid and coconut-oil during 10 days at 35°C. (level of 10.1.c [redacted]).

extraction liquid	concn. in liquid ppm		amount extracted mg per 600 cm^2
	thick material	thin material	
distilled water	< 0.5	< 0.5	< 0.2
10% ethanol	5*	< 0.5	2*
3% acetic acid	< 0.5	< 0.5	< 0.2
coconut-oil	< 0.5	< 0.5	< 0.2

* probably contamination of this sample has taken place (1)

Toxicology

Biochemical aspects

No data

Acute toxicity

No data

Subacute toxicity

No data

Semichronic toxicity

Oral

Rat

Number of animals: 5 groups of 10 ♂ and 10 ♀ (b.w. 50.6 - 53.4g)

Dosage : resp. 0, 0,03, 0.1, 0.3 and 1.0% in the diet.

Duration : 91 days

Examinations : Behaviour, appearance. Weekly growth, weekly during first 4 weeks and last 2 weeks food consuption.
At 4 weeks at all rats in 0, 0.3 and 1.0% groups and at 12 weeks on all rats in all groups blood(Hb, Ht, Er, Leu, Diff). Terminally on all rats biochemical blood values (SGOT, SGPT, SAP, seum proteins). At week 13 at all rats urine(appearance, pH, sugar, proteins, occult blood, acetone) At week 14 all rats were killed. Rel. organ wts. of all rats (10 organs). Macroscopy, Microscopy of ± 30 organs and tissues of all rats in 0 and 1.0% groups, and of liver and spleen of all rats in 0.3, 0.1 and 0.01% groups.

Abnormalities : 1.0%. Hb of ♀ at 4 weeks and Er of ♀ at 12 weeks was decreased. Blood smears of ♂ and ♀ contained normoblasts and white blood cell fragments. Rel. spleen wt. of ♂ and ♀ was increased sign. Rel. liver-, kidney- and ovary wt. of ♀ was increased sign. Rel. pituitary wt. of ♂ was increased sign. Macroscopy revealed enlayed dark spleens at ♂ and ♀.

Histology revealed changes in spleen (increased no. of cells in red pulp) and liver (Kupfer cells laden with pigment, sinusoids containing normoblasts and too many small lymhocytes) at ♂ and ♀.

0.3%. At 12 weeks decreased Ht and Er of ♀. Blood smears of ♀ contained normoblasts.

0.1%. At 12 weeks increased Ht of ♂. Sligthly decreased brain wt. of ♀.

0.03%. Slightly increased ovary wt. of ♀.

No-effect level : 0.1%

(2)

Chronic toxicity

No data

Reproduction

No data

References

1. Unpublished data of Perstop. AB Zweden
Application for the use of Trimethylolpropane in food packaging materials
Recieved June 1973

2. Unpublished report of CIVO Nr. R 3037.
[redacted].
Subchronic (90-day) toxicity study with trimethylolpropane (TMP- 99)in albino rats.
November 1969.