

ORIGINAL

**TSCA NON-CONFIDENTIAL BUSINESS INFORMATION**

DOCUMENT DESCRIPTION	DOCUMENT CONTROL NUMBER	DATE RECEIVED
8EHQ-11-18270	<b>88110000154</b>	2/28/11

COMMENTS:

**DOES NOT CONTAIN CBI**

333482



RECEIVED  
OPPT CBIC

11 FEB 28 PM 12: 29

DAX, February 25th 2011

Via DHL

8EHQ-0211-18270A

DCN: 88110000154

**TSCA Confidential Business Information Center (7407M)**

EPA East - Room 6428

Attn: TSCA Section 8(e) Coordinator

U.S. Environmental Protection Agency

1201 Constitution Avenue, NW

Washington, DC 20004-3302

Phone: 202-564-8940



**Subject: Notice in accordance with TSCA Section 8(e) - Potential adverse effects of the substance Terpeneol multi-constituent (CAS 8000-41-7)**

Dear TSCA Section 8(e) Coordinator,

By this notice, LES DERIVES RESINIQUES ET TERPENIQUES is informing you of the results of terpeneol multiconstituent studies.

This information is submitted as a precautionary measure and because it is information in which EPA may have an interest.

LES DERIVES RESINIQUES ET TERPENIQUES understands that reporting of results from this study under TSCA 8(e) is in accordance with EPA's policy.

Please send all correspondence related to this submission to my attention.

Best regards,

Emmanuelle RIALLAND  
Regulatory Affairs & REACH  
emmanuelle.rialland@drt.fr



**CONTAINS NO CBI**

**CONTAINS NO CB**

DERIVES RESINIQUES ET TERPENIQUES

RECEIVED  
OPPT CBIC

11 FEB 28 PM 12:30

# TERPINEOL MULTI-CONSTITUENT (CAS No 8000-41-7)

---

## TSCA Section 8(e) Report

Submitted to EPA :  
25<sup>th</sup> February 2011

**TABLE OF CONTENTS**

**PURPOSE FOR WHICH THIS REPORT WAS PREPARED ..... 2**

**THE ACTIVE SUBSTANCE AND BACKGROUND ..... 2**

    NAME AND ADDRESS OF THE MANUFACTURER AND OF THE PERSON REPORTING ..... 2

    SUBSTANCE IDENTITY ..... 2

    REGULATORY BACKGROUND ..... 2

**MAMMALIAN TOXICITY ..... 3**

    CONCLUSION ..... 6

**CLASSIFICATION AND LABELLING ..... 7**

    CLASSIFICATION AND LABELING: SUMMARY ..... 8

**REFERENCES ..... 9**

25<sup>th</sup> February 2011

## PURPOSE FOR WHICH THIS REPORT WAS PREPARED

Les Dérivés Résiniques et Terpéniques (DRT) are hereby delivering a report summarizing the potential adverse effects of the substance Terpineol multi-constituent (CAS 8000-41-7) in accordance with the section 8 (e) of Toxic Substance Control Act (TSCA).

## THE SUBSTANCE AND BACKGROUND

### Name and address of the manufacturer and of the person reporting

**Company:** Les Dérivés Résiniques et Terpéniques (DRT)

**Contact person:** Mme RIALLAND Emmanuelle (Regulatory Affairs)  
**Email:** [emmanuelle.rialland@drf.fr](mailto:emmanuelle.rialland@drf.fr)

**Address :** 30 Rue Gambetta – BP 206  
 40105 DAX CEDEX  
 France

**Telephone:** +33 (0)5 58 56 62 18  
**Fax:** +33 (0)5 58 56 62 40

### Substance identity

The substance Terpineol is a multi-constituent substance (mainly  $\alpha$ -Terpineol,  $\beta$ -terpineol,  $\gamma$ -Terpineol and  $\delta$ -Terpineol) having the following characteristics:

**Table 1: Substance identity**

EC number:	232-268-1
EC name:	Terpineol
CAS number (EC inventory):	8000-41-7
Molecular formula:	C <sub>10</sub> H <sub>18</sub> O
Molecular weight:	154.2493

### Regulatory Background

The registration dossier of Terpineol multi-constituent was submitted to ECHA in order to comply with REACH Regulation requirements. The registration was done by the manufacturer, Les Dérivés Résinique et Terpéniques, as lead registrant. To comply with this regulation, new toxicology studies had to be performed and the new potentially adverse findings are presented in this notice. Therefore, in this registration dossier, toxicological data were submitted including information obtained from recent toxicological studies conducted with Terpineol multi-constituent and information obtained from open scientific literature.

## MAMMALIAN TOXICITY

The toxic potential of CAS 8000-41-7 (solvent and fragrance substance) was assessed through various toxicological studies including acute toxicity studies, short-term toxicity studies, genotoxicity and reproductive toxicity studies. Other information related to Terpeneol effects was obtained from the open scientific literature and will not be reported under Section 8(e) of TSCA. These published data were included in the REACH Registration Dossier submitted to ECHA in November 2010.

In this TSCA Section 8(e) notice, DRT intends to submit the following information to EPA:

- Acute oral toxicity
- Acute inhalation toxicity
- Acute dermal toxicity
- Eye irritation
- Skin irritation
- Skin sensitization
- Repeat dose toxicity
- Mutagenicity/genotoxicity
- Reproductive/developmental toxicity screening
- Reproductive screening with 7 different Terpeneols

An acute oral toxicity study (limit test) with CAS 8000-41-7 [*Gomond P; 1998*] was conducted in rats according to OECD guideline 401. One female was found dead at day 2. In this female, congestions in the lungs, liver, spleen and kidneys were observed. Stomach and intestines were bloated by gas. In the other animals, no particular finding was identified at necropsy. Oral LD<sub>50</sub> was considered higher than 2000 mg/kg bw for males and females.

An acute dermal toxicity study of CAS 8000-41-7 (limit test) [*Richeux F; 2006a*] was conducted in rats according to OECD guideline 402. The test substance was applied to the skin by topical application for 24 h, under semi-occlusive conditions, at 2000 mg/kg bw, with a volume of 2.13 mL/kg bw. No systemic toxic effects were observed. Dermal LD<sub>50</sub> was considered higher than 2000 mg/kg for males and females.

An acute inhalation toxicity study with CAS 8000-41-7 [*Griffiths DR; 2006*] was conducted according to OECD guideline 403 in rats exposed by nose-only inhalation for 4 hours at a mean concentration of 4.76 mg/L. No mortality occurred. The LC<sub>50</sub> was considered higher than 4.76 mg/L.

A skin irritation study with CAS 8000-41-7 [*Richeux F; 2006b*] was conducted in rabbit (New Zealand White) according to OECD guideline 404 (Acute Dermal Irritation / Corrosion). The test substance CAS 8000-41-7 was applied, as supplied, at the dose of 0.5 mL, under semi-occlusive dressing during 4 hours on an undamaged skin area of 3 rabbits. Moderate erythema associated with a slight oedema was reported twenty four hours after application. These reactions were totally reversible on the 6<sup>th</sup> day of the test. Skin recovered a normal aspect between the 11<sup>th</sup> and 14<sup>th</sup> day of the test. The results indicated that the test substance CAS 8000-41-7 should be considered as irritant to the skin.

A study on eye irritation with CAS 8000-41-7 [*Richeux F; 2006c*] was conducted in rabbit (New Zealand White) according to OECD guideline 405 (Acute Eye Irritation / Corrosion). The test substance CAS 8000-41-7 was instilled pure into the eye of three rabbits at the dose

25<sup>th</sup> February 2011

of 0.1 mL. The ocular reactions observed during the study have been moderate, and totally reversible in the three animals. At the conjunctivae level, a moderate redness was noted 24 hours after the test substance instillation and was totally reversible between the 6<sup>th</sup> and 7<sup>th</sup> day of the test, associated with a moderate chemosis, noted 1 hour after the test substance instillation and totally reversible between the 5<sup>th</sup> and the 6<sup>th</sup> day of the test. At the corneal level, a moderate opacity was registered 24 hours after the test substance instillation and was totally reversible between the 3<sup>rd</sup> and the 6<sup>th</sup> day of the test. The results obtained in these experimental conditions enable to conclude that the test substance CAS 8000-41-7 was irritating to eyes.

A skin sensitization study was conducted with CAS 8000-41-7 [Richeux F; 2006d] according to OECD guideline 406. After induction (with intradermal injection at 6.25% and topical application at 100%) of 10 animals and a 17-day rest phase, the challenge consisted of a single topical application of the test substance diluted at 25% and at 12.5% in paraffin oil, under occlusive dressing for 24 hours. No macroscopic cutaneous reactions attributable to allergy were recorded in animals of the treated group with the test substance, during the examination following the removal of the occlusive dressing (challenge phase). No cutaneous intolerance reaction was recorded in animals from the negative control group. It was concluded that CAS 8000-41-7 was not a skin sensitizer.

The toxicity of Terpineol multi-constituent was evaluated in rats in a repeated dose study with doses ranging from 60 to 750 mg/kg bw/day over a period of five weeks [Thacker K; 2010]. This study was conducted according to OECD guideline 422. The liver was identified as a target organ in this study, to a greater extent in females than males. Minimal centrilobular hepatocyte hypertrophy was seen in the liver of three toxicity phase females dosed with CAS 8000-41-7 at 750 mg/kg/day for 5 weeks and accounted for the increases in liver weight at necropsy. Other biochemical findings in this study, such as bile acids and cholesterol levels in females at 750 mg/kg/day may also indicate an alteration of the metabolic function of the liver following administration of CAS 8000-41-7. However, the changes in liver weight and histopathology findings showed complete recovery after 2 weeks. The relative weight of the kidneys was higher than control in males receiving 750 mg/kg/day. Histopathological changes associated with hyaline droplets were observed in the kidneys of male rats receiving 250 or 750 mg/kg/day, but such changes are commonly associated with administration of volatile hydrocarbons and are of no consequence to human risk assessment. Testis weight was markedly low in males receiving 750 mg/kg/day and there was also an indication of low epididymal weights at this dose. Based on the findings in this study, the No-Observed-Adverse-Effect-Level (NOAEL) for males and unmated females was 250 mg/kg bw/day.

The genotoxic potential of Terpineol was assessed in bacteria and mammalian cells. Terpineol was assayed for mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium* [Marchal P; 2006], both in the absence and in the presence of metabolic activation by induced rat liver post-mitochondrial fraction (S-9), in two separate experiments. Terpineol did not induce mutation in these five histidine-requiring strains of *Salmonella typhimurium*. Alpha-terpineol (CAS 98-55-5) was also found negative in several Ames tests conducted in histidine-requiring strains (TA98, TA100, TA1535, TA1537, TA 1538 and TA102) of *Salmonella typhimurium*. These studies were conducted according to OECD guideline 471 [Heck JD; 1989 - Gomes-Carneiro; 1998 - Seifried HE; 2006]. Terpineol CAS 8000-41-7 was also tested in an *in vitro* chromosome aberration test according to OECD guideline 473, by using duplicate human primary lymphocyte cultures prepared from the pooled blood of three male donors in two independent

25<sup>th</sup> February 2011

experiments [Lloyd M; 2010]. No increases in the frequency of cells with numerical aberrations, which exceeded the concurrent controls and the normal ranges, were observed in cultures treated with Terpineol (CAS No. 8000-41-7) in the absence and presence of S-9. It was concluded that Terpineol (CAS No. 8000-41-7) did not induce chromosome aberrations in the absence or presence of metabolic activation (S-9) when tested up to toxic concentrations. Other information available in open scientific literature confirms the absence of genotoxic activity of Terpineol [Seifried HE; 2006].

The systemic toxic potential, including reproductive effects, of Terpineol (CAS No. 8000-41-7) was assessed in Sprague Dawley rats by oral gavage administration over a period of five weeks at doses of 0, 60, 250 or 750 mg/kg/day [Thacker K; 2010] and according to OECD guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test). This study indicated that the kidneys, the liver and the testes were the main target organs. Reproductive endpoints of oestrous cycles, pre coital interval, mating performance and fertility were not affected by administration of Terpineol CAS 8000-41-7 up to 250 mg/kg/day. There were no adverse effects on survival, growth and development of offspring up to Day 7 of age. Testis weight was markedly low compared to control in males receiving 750 mg/kg/day and there was also an indication of low epididymal weights at this dose. Reduced numbers or complete absence of spermatozoa accompanied by the presence of degenerate spermatogenic cells in ducts were observed in the epididymides of males receiving 750 mg/kg/day at the end of the 5 week dosing period. None of these effects were observed at 250 mg/kg/day. The gavage administration is a normal way to evaluate drug toxicity (which can be administered as one dose/day) or a convenient surrogate (no need to mix with diet) to evaluate toxicity which could occur due to presence of the substance in the food or to extrapolate to different routes of exposure (dermal or inhalation). However, in some cases, it creates pharmacokinetic (and then pharmacodynamic) circumstances which cannot be encountered in real conditions of exposure and can be considered in this case as a non-relevant route of exposure (as would be IV or IP mode of administration). In the reproduction toxicity screening test, the effects on testes may be related to a peak plasma level which is much higher after the rapid gavage administration. In order to confirm the hypothesis of a bolus effect, a screening study was performed to investigate the potential toxic effect of Terpineol CAS 8000-41-7 when administered by diet versus by gavage [Vijaykumar B; 2010]. The purpose of this screening study was also to compare, the toxicological profiles of seven different terpineols when administered by gavage route. Groups of five male rats (Sprague Dawley) were administered by gavage 500 and 750 mg/kg/day of Terpineol CAS 8000-41-7 with variable compositions, alpha-Terpineol (CAS 98-55-5 and CAS 10482-56-1) or beta-Terpineol (CAS 138-87-4); two additional groups were fed with a level sufficient of Terpineol CAS 8000-41-7 to achieve a dosage around 500 and 750 mg/kg/day during a period long enough to compare gavage and diet administration. Similar effects on the liver were reported in all treated animals whatever the route of administration (i.e. marked dose-related increase in liver weight). On the contrary, effects on testis weight and sperm motility were observed in gavage groups receiving alpha-Terpineol (CAS 98-55-5 and CAS 10482-56-1) and to a lesser extent Terpineol CAS 8000-41-7, but no effects were observed on this parameter in animals from the diet groups and in animals treated with beta-Terpineol (CAS 138-87-4) by gavage. There are therefore strong arguments to consider that the testicular effects observed at 750 mg/kg/day after gavage administration were due to a peak effect of Terpineol and are unlikely to occur, even at the highest achievable dose, by either inhalation, dermal or oral route (in the food).

25<sup>th</sup> February 2011

## Conclusion

The conclusions laid down in this report were derived on the basis of evaluation of the toxicological studies conducted with Terpineol CAS 8000-41-7, and in some cases with alpha-terpineol CAS 98-55-5 and 10482-56-1 and beta-terpineol CAS 138-87-4. Additional information obtained from the open scientific literature was not included in this report as according to the TSCA Section 8(e) Reporting Guide, the Agency considers to be adequately informed already.

The acute toxicity information shows that Terpineol CAS 8000-41-7 is irritant to skin and irritant to eyes when tested in New Zealand White rabbits in studies conducted according to OECD guideline 404 and 405. No other effects were identified in acute toxicity studies. In sub-chronic toxicity study and reproduction/ developmental toxicity screening test, the target organs identified were the liver, the kidney and the testes at top dose. The effects on the testis weight and sperm parameters were clearly identified as related to the bolus effect generated by the oral gavage administration. Similar study conducted with animals receiving Terpineol CAS 8000-41-7 by diet at sufficient levels to achieve a dosage at 500 and 750 mg/kg did not show any effect on the testis, whereas effects on the liver were clearly reproduced. The liver was identified as a target organ in this study, to a greater extent in females than males. However, the changes in liver weight and histopathology findings showed complete recovery after 2 weeks, and the changes are therefore considered to be an adaptive change, thus considered to be not adverse in the context of the duration of this study. The bodyweight-relative kidney weights of males at 750 mg/kg/day were above the Control value; this finding was associated with moderate cortical tubules with hyaline droplets in the kidneys of males receiving 250 and 750 mg/kg/day. Hyaline droplet formation is commonly seen in mature male rats after administration of certain chemicals. The protein droplets are considered to be the result of the accumulation of  $\alpha$ 2-microglobulin within the tubular cell lysosomes in the kidney, mechanism not found in female rats or humans. The effects on male kidneys were therefore considered of no toxicological concern. Based on the findings in this study, the No-Observed-Adverse-Effect-Level (NOAEL) for unmated females was 250 mg/kg/day, the NOAEL for male reproductive toxicity was 250 mg/kg/day and the NOAEL for maternal and developmental toxicity was at least 250 mg/kg/day.

## CLASSIFICATION AND LABELLING

Acute oral and dermal toxicity studies (limit test) with CAS 8000-41-7 were conducted in Sprague-Dawley rats following OECD guidelines 401 and 402. Under the conditions used in these studies, oral and dermal LD50 of the test substance were higher than 2000 mg/kg bw for males and females.

Acute inhalation toxicity study with CAS 8000-41-7 was conducted in Sprague-Dawley rats following OECD guideline 403. No mortality occurred: LC50 was considered to be greater than 4.76 mg/L.

Under the test conditions used in the above studies, and according to the GHS criteria the test substance CAS 8000-41-7 should not be classified for oral, dermal and inhalation acute toxicity.

Although Terpineol (CAS No 8000-41-7) was not irritant to human skin, it was found to be irritant to skin in a study conducted according to OECD guideline 404. Terpineol was found to be irritant to eyes in a GLP study conducted according to OECD guideline 405. Therefore, according to the GSH criteria the test substance CAS 8000-41-7 should be classified as irritating to skin category 2 and as irritating to eyes category 2.

Terpineol CAS 8000-41-7 and alpha-Terpineol were found negative in Ames tests conducted according to OECD guideline 471, with and without metabolic activation. Terpineol was also found negative in a recent GLP chromosome aberration test in primary cultures of human lymphocytes conducted according to OECD guideline 473. Alpha-terpineol was negative in a gene mutation test conducted similarly to OECD guideline 476 using mouse lymphoma tk<sup>+</sup>/L5178Y cells with and without metabolic activation. Terpineol CAS 8000-41-7 was therefore considered as non-mutagenic and should not be classified as mutagenic according to the GHS criteria.

The toxic effects reported in the repeated dose toxicity study were seen to occur at 750 mg/kg bw/day in males (liver and testes) and in a lesser extent in females (liver) (i.e. at least at dose level >250 mg/kg/day). Terpineol (CAS 8000-41-7) is therefore not classified according to GHS criteria.

25<sup>th</sup> February 2011

## Classification and Labeling: Summary

### Classification

Acute toxicity - oral:	No classification
Acute toxicity - dermal:	No classification
Acute toxicity - inhalation:	No classification
Skin corrosion/irritation:	Skin Irrit.2 (Hazard statement: H315: Causes skin irritation.)
Serious damage/eye irritation:	Eye Irrit. 2 (Hazard statement: H319: Causes serious eye irritation.)
Respiration sensitization:	No classification
Skin sensitization:	No classification
Aspiration hazard:	No classification
Reproductive Toxicity:	No classification
Reproductive Toxicity: Effects on or via lactation:	No classification
Germ cell mutagenicity:	No classification
Carcinogenicity:	No classification

### Labelling

Signal word: Warning

#### Hazard pictogram:

GHS07: exclamation mark



#### Hazard statements:

H315: Causes skin irritation.

H319: Causes serious eye irritation.

#### Precautionary statements:

P280: Wear protective gloves/protective clothing/eye protection/face protection.

P302+P352: IF ON SKIN: Wash with plenty of soap and water.

P332+P313: If skin irritation occurs: Get medical advice/attention.

P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

P337+P313: If eye irritation persists: Get medical advice/attention.

P501: Dispose of contents/container to...

25<sup>th</sup> February 2011**REFERENCES**

- Gomond P (1998). CAS 8000-41-7: Acute oral toxicity – Sponsor DRT- GLP - Unpublished study report.
- Griffiths DR (2006). CAS 8000-41-7: Acute Inhalation toxicity – Sponsor DRT- GLP - Unpublished study report.
- Richeux F (2006a). CAS 8000-41-7: Acute Dermal toxicity – Sponsor DRT- GLP - Unpublished study report.
- Richeux F. (2006b). CAS 8000-41-7: Acute skin Irritation – Sponsor DRT- GLP - Unpublished study report.
- Richeux F. (2006c). CAS 8000-41-7: Acute Eye Irritation – Sponsor DRT- GLP - Unpublished study report.
- Richeux F. (2006d). CAS 8000-41-7: Skin Sensitization– Sponsor DRT- GLP - Unpublished study report.
- Marchal P. (2006). CAS 8000-41-7: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*. Sponsor DRT- GLP - Unpublished study report.
- Heck JD, Vollmuth TA, Cifone MA, Jagannath DR, Myhr B and Curren RD (1989). An evaluation of food flavoring ingredients in a genetic toxicity screening battery. *The Toxicologist* 9 (1), 257.
- Gomes-Carneiro MR, Felzenszwalb I and Paumgarten FJR. (1998). Mutagenicity testing of ( $\pm$ )camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the *Salmonella*/microsome assay. *Mutation Research* 416: 129-136.
- Lloyd M (2010). CAS 8000-41-7: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes– Sponsor DRT- GLP - Unpublished study report.
- Seifried HE, Seifried RM, Clarke J J, Junghans TB, San RHC (2006). A compilation of two decades of mutagenicity test results with the Ames *Salmonella typhimurium* and L5178Y mouse lymphoma cell mutation assays. *Chemical Research of Toxicology*, 19(5):627-644.
- Thacker K (2010). CAS 8000-41-7: Combined Repeat Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Study in the Rat – Sponsor DRT - GLP - Unpublished study report.
- Vijaykumar B. Malashetty (2011). Investigative Toxicity Study to Compare Effects by Dietary Administration and Oral Gavage Administration for 2 weeks in Male CD Rats. Sponsor DRT China - GLP - Unpublished study report.

**COPY  
DON'T STICK!**

**\* ARCHIVE DOC \***  
Not to be attached to package



From DRT  
VALERIE LANOT 33 5 58 56 62 00  
30 RUE GAMBETTA  
40105 DAX  
FR France

Origin  
BIQ

To TSCA CONFIDENTIAL BUSINESS INFO  
TSCA SECTION 8(e) COORDINATOR  
EPA EAST - ROOM 6428  
U.S. ENVIRONMENTAL PROTECTION  
AGENCY 1201 CONSTITUTION AVENU  
20004 3302 WASHINGTON  
Washington,DC  
US United States of America

Phone:  
2025648940

**US-DCA-DCA**

Day Time



Ref code DOC/VL  
Account No 220171483

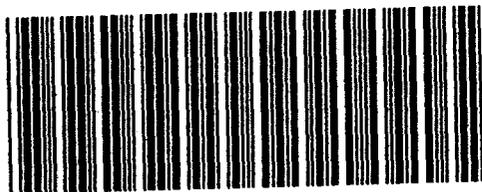
Total Weight: 0.5 kg  
Vol Weight: 0  
Pickup date: 2011-02-25

Piece  
1

Content / Commerce Control Statement / RC

DOCUMENTS

Service : DAP Customs Value : 0.00 EUR  
Imp/Exp Type : permanent IV : 0.00 EUR



WAYBILL 70 7984 2626

JD00 00 8330 0323 2912

EXPRESS WORLDWIDE



From DRT  
VALERIE LANOT 33 5 58 56 62 00  
30 RUE GAMBETTA  
40105 DAX  
FR France

Origin  
BIQ

To TSCA CONFIDENTIAL BUSINESS INFO  
TSCA SECTION 8(e) COORDINATOR  
EPA EAST - ROOM 6428  
U.S. ENVIRONMENTAL PROTECTION  
AGENCY 1201 CONSTITUTION AVENU  
20004 3302 WASHINGTON  
Washington,DC  
US United States of America

Phone:  
2025648940

CENTER

**US-DCA-DCA**

Day Time



Ref code DOC/VL  
Account No 220171483

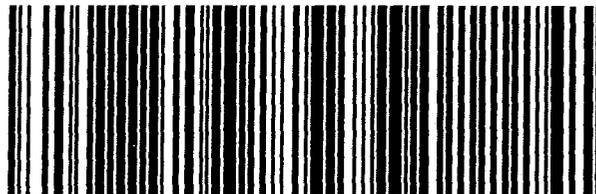
Piece Weight: 0.5 kg  
Pickup date: 2011-02-25

Piece  
1/1

Content / Commerce Control Statement / RC  
DOCUMENTS



WAYBILL 70 7984 2626



(2L)US20004+42000000



(J)JD 0000 8330 0323 2912