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Iodixanol,
Iotrolan, Iohexol,
Iopenol, Ioversol, Iopamidol
and Iopromid-Determination
of the n-Octanol/
Water Partition Coefficient

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Main Office	Regional Office, Sørlandet	Regional Office, Østlandet	Regional Office, Vestlandet	Akvaplan-NIVA A/S
P.O. Box 173, Kjelsås	Televeien 1	Rute 866	Thormøhlensgt 55	Søndre Tollbugate 3
N-0411 Oslo	N-4890 Grimstad	N-2312 Ottestad	N-5008 Bergen	N-9000 Tromsø
Norway	Norway	Norway	Norway	Norway
Phone (47) 22 18 51 00	Phone (47) 37 04 30 33	Phone (47) 62 57 64 00	Phone (47) 55 32 56 40	Phone (47) 77 68 52 80
Telefax (47) 22 18 52 00	Telefax (47) 37 04 45 13	Telefax (47) 62 57 66 53	Telefax (47) 55 32 88 33	Telefax (47) 77 68 05 09

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Abstract:
The octanol/water partition coefficient is determined for 7 different pharmaceuticals using the FDA method number 3.02. Description of the method, example chromatograms and results are presentet.
All the log P _{ow} values determined are below 1, and the test compounds do not have potential to bioaccumulate or to sorb onto organic particles.


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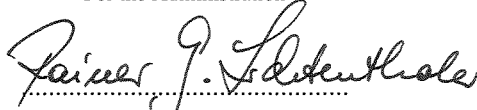
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Project manager


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Torgunn Sætre

For the Administration


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Summary

Iodixanol, Iotrolan, Iohexol, Iopentol, Ioversol, Iopamidol and Iopromid - Determination of the n-Octanol/Water Partition Coefficient

Sponsor:	Nycomed Imaging
Report title:	Iodixanol, Iotrolan, Iohexol, Iopentol, Ioversol, Iopamidol and Iopromid - Determination of the n-Octanol/Water Partition Coefficient.
Lab code:	B166/1 to B166/7
Test articles:	-Iodixanol, lab code B166/1 -Iotrolan, lab code B166/2 -Iohexol, lab code B166/3 -Iopentol, lab code B166/4 -Ioversol, lab code B166/5 -Iopamidol, lab code B166/6 -Iopromid, lab code B166/7
Experimental test dates:	3 January to 12 January 1995
Results:	Iodixanol was determined at 1.00×10^{-3} M and 1.0×10^{-4} M to have a mean $\log P_{ow}$ value < 1 . Iotrolan was determined at 9.95×10^{-4} M and 9.95×10^{-5} M to have a mean $\log P_{ow}$ value < 1 Iohexol was determined at 9.95×10^{-4} M and 9.95×10^{-5} M to have a mean $\log P_{ow}$ value < 1 Iopentol was determined at 9.88×10^{-4} M and 9.88×10^{-5} M to have a mean $\log P_{ow}$ value < 1 Ioversol was determined at 1.01×10^{-3} M and 1.01×10^{-4} M to have a mean $\log P_{ow}$ value < 1 Iopamidol was determined at 9.94×10^{-4} M and 9.94×10^{-5} M to have a mean $\log P_{ow}$ value < 1 Iopromid was determined at 9.85×10^{-4} M and 9.85×10^{-5} M to have a mean $\log P_{ow}$ value < 1
Conclusions:	Based solely on these P_{ow} values, the seven different pharmaceuticals do not have potential to bioaccumulate or to sorb onto organic particles.

1. Introduction

The objective of this study was to determine the n-octanol/water partition coefficient for Iodixanol, Iotrolan, Iohexol, Iopentol, Ioversol, Iopamidol and Iopromid by the shake-flask method as originally described by Leo et. al. (1971).

The study was initiated on 2 January 1995, and was completed the day the final report was signed. The experimental work was run out in the laboratories at the Norwegian Institute for Water Research in the period from 3 to 12 January 1995. All original data generated from this study and the final report are stored at the above location.

2. Methods

2.1 Partition test method

This study was conducted according to the Food and Drug Administration Technical Assistance Handbook Section 3.02, n-Octanol/Water Partition Coefficient.

2.2 Saturation of the solvents

In an Erlenmeyer flask, 500 ml of n-octanol (Merck, Lot No K17703191) and 25 ml of distilled water were combined. In a separatory funnel 2000 ml of distilled water and 50 ml of n-octanol were combined. Both the Erlenmeyer flask and the separatory funnel were placed on a shaker table, and shaken at approximately 125 revolutions per minute (rpm) for 24 hours to saturate both phases. The phases were allowed to stand long enough to separate before used in the test.

2.3 Test System

The test system used in this study consisted of 125 ml glass centrifuge tubes. During the test the centrifuge tubes were placed on a shaker table in a thermostated chamber held at 25 ± 1 °C. The samples were maintained in the dark to minimise the potential for photo chemical degradation of the test article.

3. Calculations

The partition coefficient (P_{ow}) for the test chemical was calculated by dividing the molar concentration of the test chemical in n-octanol by the molar concentration of the test chemical in water. The P_{ow} was calculated from the following equation:

$$P_{ow} = \frac{C_{\text{octanol}}}{C_{\text{water}}}$$

where C_{octanol} was the molar concentration in n-octanol and C_{water} was the molar concentration in water.

Mass balance was calculated for each test system in the partitioning phase by summing the quantities obtained from both phases.

4. Test Articles

All the test articles received in brown glass bottles were stored at room temperature.

5. Iodixanol

5.1 Description of the test article

-Iodixanol, lab code B166/1

Empirical formula: $C_{35}H_{44}I_6N_6O_{15}$

Molecular weight: 1550.2

Physical appearance: Amorphous, crystalline white powder

B. Nr: 104203 (18)

CAS number: 92339-11-2

Melting point: Decomposing 245-265 °C

5.2 Analytical Conditions

Instrument: Waters HPLC with a Waters 490 Programmable Multiwavelength Detector.

Column: Waters C-18 Novapack 3.9 x 150 mm

Temperature: 25 °C

Flow: 0.7 ml/min

Detector: 254 nm, 0.05 AUFS

Mobile Phase: Acetonitrile/water 9:91 (v/v)

5.3 Test solution preparation

5.3.1 Stock solution.

A stock solution was prepared for preliminary testing by adding 387.63 mg to a 250.0 ml volumetric flask and dissolving and diluting to volume with n-octanol saturated water. This produced a stock solution of 1.00×10^{-3} M.

5.3.2 Test solution.

The stock solution was used as test solution with a concentration of 1.00×10^{-3} M in n-octanol saturated water. 25.0 ml of the stock solution was diluted with n-octanol saturated water to 250.0 ml to prepare a test solution with a concentration of 1.00×10^{-4} M.

5.4 Test Procedure.

The partitioning study was conducted at two nominal concentrations: approximate 0.001 M and 0.0001M in n-octanol saturated water. Triplicate test systems were prepared in 125 ml centrifuge tubes by equilibrating 50.0 ml water containing Iodixanol with 25.0 ml n-octanol. The centrifuge tubes were sealed, shaken vigorously and placed on a shaking table at approximate 150 rpm in a thermostated chamber and maintained in the dark at 25 ± 1 °C. The tubes were shaken for one hour, and were standing overnight in the chamber.

The tubes were centrifuged at 25 °C for 10 min at 3500 rpm and sampled. 20.0 ml of the n-octanol phase was transferred to another tube, and shaken with 2.0 ml of n-octanol saturated water for 20 min. The tubes were centrifuged for 10 min at 3500 rpm, samples were taken from the water phase and designated as the n-octanol phase samples. After removal of the n-octanol from the initial samples, the water phase (lower layer) of each replicate of the test article was delivered into a HPLC vial. n-Octanol and water blanks were treated in the same way as the samples. Samples were analysed by HPLC according to the methodology presented in Analytical Conditions

5.5 Results

Nominal concentrations of approximate 0.001 M and 0.0001 M in n-octanol saturated water were selected for partitioning testing. The concentration of Iodixanol measured in each replicate n-octanol or aqueous phase in the partitioning study is presented in Table 1, page 22.

The partition coefficient, P_{ow} , values for Iodixanol determined at concentrations of 1.00×10^{-3} M and 1.00×10^{-4} M were 5.01×10^{-4} and 3.63×10^{-4} , respectively with corresponding $\log P_{ow}$ values of -3.30 and -3.44. Each mean P_{ow} represents the average of three values obtained at each concentration. Iodixanol was shown to partition slightly into the n-octanol phase. Mass balance values (% recovery) ranged from 91.7 % to 98.5 %, and are presented in Table 2, page 22. The temperature inside the thermostated chamber ranged from 25.1 to 25.2 °C during partitioning testing.

5.6 Conclusions

Based on the test results, Iodixanol will not bioaccumulate or sorb onto organic particles. The n-octanol/water partition coefficient is outside the range of the test method, and should be presented as $\log P_{ow} < 1$.

6. Iotrolan

6.1 Description of the test article

-Iotrolan, lab code B166/2

Empirical formula: $C_{37}H_{48}I_6N_6O_{18}$

Molecular weight: 1626.25

Physical appearance: White powder

J. Nr: 1546/23-3

6.2 Analytical Conditions

Instrument: Waters HPLC with a Waters 490 Programmable Multiwavelength Detector.

Column: Waters C-18 Novapack 3.9 x 150 mm

Temperature: 25 °C

Flow: 0.7 ml/min

Detector: 254 nm, 0.05 AUFS

Mobile Phase: Acetonitrile/water 5.4:94.6 (v/v)

6.3 Test solution preparation

6.3.1 Stock solution.

A stock solution was prepared for preliminary testing by adding 404.71 mg to a 250.0 ml volumetric flask and dissolving and diluting to volume with water saturated with n-octanol. This produced a stock solution of 9.95×10^{-4} M.

6.3.2 Test solution.

The stock solution was used as test solution with a concentration of 9.95×10^{-4} M in n-octanol saturated water. 25.0 ml of the stock solution was diluted with n-octanol saturated water to 250.0 ml to prepare a test solution with a concentration of 9.95×10^{-5} M.

6.4 Test Procedure.

The partitioning study was conducted at two nominal concentrations: approximate 0.001 M and 0.0001M in n-octanol saturated water. Triplicate test systems were prepared in 125 ml centrifuge tubes by equilibrating 50.0 ml water containing Iotrolan with 25.0 ml n-octanol. The centrifuge tubes were sealed, shaken vigorously and placed on a shaking table at approximate 150 rpm in a thermostated chamber and maintained in the dark at 25 ± 1 °C. The tubes were shaken for one hour, and were standing overnight in the chamber.

The tubes were centrifuged at 25 °C for 10 min at 3500 rpm and sampled. 20.0 ml of the n-octanol phase was transferred to another tube, and shaken with 2.0 ml of n-octanol saturated water for 20 min. The tubes were centrifuged for 10 min at 3500 rpm, samples were taken from the water phase and designated as the n-octanol phase samples. After removal of the n-octanol from the initial samples, the water phase (lower layer) of each replicate of the test article was delivered into a HPLC vial. n-Octanol and water blanks were treated in the same way as the samples. Samples were analysed by HPLC according to the methodology presented in Analytical Conditions

The concentration in the octanol phase in the 0.0001 M test system was too low to be detected. The test was repeated shaking 25 ml of water containing Iotrolan with 100 ml of n-octanol in 125 ml centrifugation tubes. 90 ml of the n-octanol phase was extracted with 2 ml of water

after the equilibration. This was taken as the n-octanol sample.

6.5 Results

Nominal concentrations of approximate 0.001 M and 0.0001 M in n-octanol saturated water were selected for partitioning testing. The concentration of Iotrolan measured in each replicate n-octanol or aqueous phase in the partitioning study is presented in Table 3, page 23.

The partition coefficient, P_{ow} , values for Iotrolan determined at concentrations of 9.95×10^{-4} M and 9.95×10^{-5} M were 6.03×10^{-5} and 6.17×10^{-5} , respectively with corresponding $\log P_{ow}$ values of -4.22 and -4.21. Each mean P_{ow} represents the average of three values obtained at each concentration. Iotrolan was shown to partition slightly into the n-octanol phase. Mass balance values (% recovery) ranged from 94.8 % to 102.1 %, and are presented in Table 4, page 23. The temperature inside the thermostated chamber ranged from 25.1 to 25.2 °C during partitioning testing.

6.6 Conclusions

Based on the test results, Iotrolan will not bioaccumulate or sorb onto organic particles. The n-octanol/water partition coefficient is outside the range of the test method, and should be presented as $\log P_{ow} < 1$.

7. Iohexol

7.1 Description of the test article

-Iohexol, lab code B166/3

Empirical formula: $C_{19}H_{26}I_3N_3O_9$

Molecular weight: 821.44

Physical appearance: White powder

B. Nr: 206017

CAS number: 66108-95-0

Melting point: 177-187 °C

7.2 Analytical Conditions

Instrument: Waters HPLC with a Waters 490 Programmable Multiwavelength Detector.

Column: Waters C-18 Novapack 3.9 x 150 mm

Temperature: 25 °C

Flow: 0.7 ml/min

Detector: 254 nm, 0.05 AUFS

Mobile Phase: Acetonitrile/water 5.4:94.6 (v/v)

7.3 Test solution preparation

7.3.1. Stock solution.

A stock solution was prepared for preliminary testing by adding 204.27 mg to a 250.0 ml volumetric flask and dissolving and diluting to volume with n-octanol saturated water. This produced a stock solution of 9.95×10^{-4} M.

7.3.2 Test solution.

The stock solution was used as test solution with a concentration of 9.95×10^{-4} M in n-octanol saturated water. 25.0 ml of the stock solution was diluted with n-octanol saturated water to 250.0 ml to prepare a test solution with a concentration of 9.95×10^{-5} M.

7.4 Test Procedure.

The partitioning study was conducted at two nominal concentrations: approximate 0.001 M and 0.0001M in n-octanol saturated water. Triplicate test systems were prepared in 125 ml centrifuge tubes by equilibrating 50.0 ml water containing Iohexol with 25.0 ml n-octanol. The centrifuge tubes were sealed, shaken vigorously and placed on a shaking table at approximate 150 rpm in a thermostated chamber and maintained in the dark at 25 ± 1 °C. The tubes were shaken for one hour, and were standing overnight in the chamber.

The tubes were centrifuged at 25 °C for 10 min at 3500 rpm and sampled. 20.0 ml of the n-octanol phase was transferred to another tube, and shaken with 2.0 ml of n-octanol saturated water for 20 min. The tubes were centrifuged for 10 min at 3500 rpm, samples were taken from the water phase and designated as the n-octanol phase samples. After removal of the n-octanol from the initial samples, the water phase (lower layer) of each replicate of the test article was delivered into a HPLC vial. n-Octanol and water blanks were treated in the same way as the samples. Samples were analysed by HPLC according to the methodology presented in Analytical Conditions

7.5 Results

Nominal concentrations of approximate 0.001 M and 0.0001 M in n-octanol saturated water were selected for partitioning testing. The concentration of Iohexol measured in each replicate n-octanol or aqueous phase in the partitioning study is presented in Table 5, page 24.

The partition coefficient, P_{ow} , values for Iohexol determined at concentrations of 9.95×10^{-4} M and 9.95×10^{-5} M were 6.46×10^{-4} and 4.37×10^{-4} , respectively with corresponding $\log P_{ow}$ values of -3.19 and -3.36. Each mean P_{ow} represents the average of three values obtained at each concentration. Iohexol was shown to partition slightly into the n-octanol phase. Mass balance values (% recovery) ranged from 76.2 % to 88.1 %, and are presented in Table 6, page 24. The temperature inside the thermostated chamber ranged from 25.1 to 25.3 °C during partitioning testing.

7.6 Conclusions

Based on the test results, Iohexol will not bioaccumulate or sorb onto organic particles. The octanol/water partition coefficient is outside the range of the test method, and should be presented as $\log P_{ow} < 1$.

8. Iopentol

8.1 Description of the test article:

-Iopentol, lab code B166/4

Empirical formula: $C_{20}H_{28}I_3N_3O_9$

Molecular weight: 835.16

Physical appearance: White powder

B. Nr: 409169

CAS number: 89797-00-2

Melting point: 144-159 °C

8.2 Analytical Conditions

Instrument: Waters HPLC with a Waters 490 Programmable Multiwavelength Detector.

Column: Waters C-18 Novapack 3.9 x 150 mm

Temperature: 25 °C

Flow: 0.7 ml/min

Detector: 254 nm, 0.05 AUFS

Mobile Phase: Acetonitrile/water 8.1:91.9 (v/v)

8.3 Test solution preparation

8.3.1 Stock solution.

A stock solution was prepared for preliminary testing by adding 206.23 mg to a 250.0 ml volumetric flask and dissolving and diluting to volume with n-octanol saturated water. This produced a stock solution of 9.88×10^{-4} M.

8.3.2 Test solution.

The stock solution was used as test solution with a concentration of 9.88×10^{-4} M in n-octanol saturated water. 25.0 ml of the stock solution was diluted with n-octanol saturated water to 250.0 ml to prepare a test solution with a concentration of 9.88×10^{-5} M.

8.4 Test Procedure.

The partitioning study was conducted at two nominal concentrations: approximate 0.001 M and 0.0001M in n-octanol saturated water. Triplicate test systems were prepared in 125 ml centrifuge tubes by equilibrating 50.0 ml water containing Iopentol with 25.0 ml n-octanol. The centrifuge tubes were sealed, shaken vigorously and placed on a shaking table at approximate 150 rpm in a thermostated chamber and maintained in the dark at 25 ± 1 °C. The tubes were shaken for one hour, and were standing overnight in the chamber.

The tubes were centrifuged at 25 °C for 10 min at 3500 rpm and sampled. 20.0 ml of the n-octanol phase was transferred to another tube, and shaken with 2.0 ml of n-octanol saturated water for 20 min. The tubes were centrifuged for 10 min at 3500 rpm, samples were taken from the water phase and designated as the n-octanol phase samples. After removal of the n-octanol from the initial samples, the water phase (lower layer) of each replicate of the test article was delivered into a HPLC vial. n-Octanol and water blanks were treated in the same way as the samples. Samples were analysed by HPLC according to the methodology presented in Analytical Conditions

8.5 Results

Nominal concentrations of approximate 0.001 M and 0.0001 M in n-octanol saturated water were selected for partitioning testing. The concentration of Iopentol measured in each replicate n-octanol or aqueous phase in the partitioning study is presented in Table 7, page 25.

The partition coefficient, P_{ow} , values for Iopentol determined at concentrations of 9.88×10^{-4} M and 9.88×10^{-5} M were 4.37×10^{-4} and 2.75×10^{-4} , respectively with corresponding $\log P_{ow}$ values of -3.36 and -3.56. Each mean P_{ow} represents the average of three values obtained at each concentration. Iopentol was shown to partition slightly into the n-octanol phase. Mass balance values (% recovery) ranged from 95.9 % to 104.1 %, and are presented in Table 8, page 25. The temperature inside the thermostated chamber was 25.3 °C during partitioning testing.

8.6 Conclusions

Based on the test results, Iopentol will not bioaccumulate or sorb onto organic particles. The octanol/water partition coefficient is outside the range of the test method, and should be presented as $\log P_{ow} < 1$.

9. Ioversol

9.1 Description of the test article

-Ioversol, lab code B166/5

Empirical formula: $C_{18}H_{24}I_3N_3O_9$

Molecular weight: 807.12

Physical appearance: White powder

J. Nr: 1334/31-1

9.2 Analytical Conditions

Instrument: Waters HPLC with a Waters 490 Programmable Multiwavelength Detector.

Column: Waters C-18 Novapack 3.9 x 150 mm

Temperature: 25 °C

Flow: 0.7 ml/min

Detector: 254 nm, 0.05 AUFS

Mobile Phase: Acetonitrile/water 3.6:96.4 (v/v)

9.3 Test solution preparation

2.3.5 Stock solution.

A stock solution was prepared for preliminary testing by adding 203.22 mg to a 250.0 ml volumetric flask and dissolving and diluting to volume with n-octanol saturated water. This produced a stock solution of 1.01×10^{-3} M.

2.3.5 Test solution.

The stock solution was used as test solution with a concentration of 1.01×10^{-3} M in n-octanol saturated water. 25.0 ml of the stock solution was diluted with n-octanol saturated water to 250.0 ml to prepare a test solution with a concentration of 1.01×10^{-4} M.

9.4 Test Procedure.

The partitioning study was conducted at two nominal concentrations: approximate 0.001 M and 0.0001M in n-octanol saturated water. Triplicate test systems were prepared in 125 ml centrifuge tubes by equilibrating 50.0 ml water containing Ioversol with 25.0 ml n-octanol. The centrifuge tubes were sealed, shaken vigorously and placed on a shaking table at approximate 150 rpm in a thermostated chamber and maintained in the dark at 25 ± 1 °C. The tubes were shaken for one hour, and were standing overnight in the chamber.

The tubes were centrifuged at 25 °C for 10 min at 3500 rpm and sampled. 20.0 ml of the n-octanol phase was transferred to another tube, and shaken with 2.0 ml of n-octanol saturated water for 20 min. The tubes were centrifuged for 10 min at 3500 rpm, samples were taken from the water phase and designated as the n-octanol phase samples. After removal of the n-octanol from the initial samples, the water phase (lower layer) of each replicate of the test article was delivered into a HPLC vial. n-Octanol and water blanks were treated in the same way as the samples. Samples were analysed by HPLC according to the methodology presented in Analytical Conditions

9.5 Results

Nominal concentrations of approximate 0.001 M and 0.0001 M in n-octanol saturated water were selected for partitioning testing. The concentration of Ioversol measured in each replicate n-octanol or aqueous phase in the partitioning study is presented in Table 9, page 26.

The partition coefficient, P_{ow} , values for Ioversol determined at concentrations of 1.01×10^{-3} M and 1.01×10^{-4} M were 2.04×10^{-4} and 1.17×10^{-4} , respectively with corresponding $\log P_{ow}$ values of -3.69 and -3.93. Each mean P_{ow} represents the average of three values obtained at each concentration. Ioversol was shown to partition slightly into the n-octanol phase. Mass balance values (% recovery) ranged from 93.0 % to 100.8 %, and are presented in Table 10, page 26. The temperature inside the thermostated chamber ranged from 25.3 to 25.4 °C during partitioning testing.

9.6 Conclusions

Based on the test results, Ioversol will not bioaccumulate or sorb onto organic particles. The octanol/water partition coefficient is outside the range of the test method, and should be presented as $\log P_{ow} < 1$.

10. Iopamidol

10.1 Description of the test article

-Iopamidol, lab code B166/6

Empirical formula: $C_{17}H_{22}I_3N_3O_8$

Molecular weight: 777.09

Physical appearance: White powder

J. Nr: 1104/21-1

10.2 Analytical Conditions

Instrument: Waters HPLC with a Waters 490 Programmable Multiwavelength Detector.

Column: Waters C-18 Novapack 3.9 x 150 mm

Temperature: 25 °C

Flow: 0.7 ml/min

Detector: 254 nm, 0.05 AUFS

Mobile Phase: Acetonitrile/water 3.6:96.4 (v/v)

10.3 Test solution preparation

10.3.1 Stock solution.

A stock solution was prepared for preliminary testing by adding 193.15 mg to a 250.0 ml volumetric flask and dissolving and diluting to volume with n-octanol saturated water. This produced a stock solution of 9.94×10^{-4} M.

10.3.2 Test solution.

The stock solution was used as test solution with a concentration of 9.94×10^{-4} M in n-octanol saturated water. 25.0 ml of the stock solution was diluted with n-octanol saturated water to 250.0 ml to prepare a test solution with a concentration of 9.94×10^{-5} M.

10.4 Test Procedure.

The partitioning study was conducted at two nominal concentrations: approximate 0.001 M and 0.0001M in n-octanol saturated water. Triplicate test systems were prepared in 125 ml centrifuge tubes by equilibrating 50.0 ml water containing Iopamidol with 25.0 ml n-octanol. The centrifuge tubes were sealed, shaken vigorously and placed on a shaking table at approximate 150 rpm in a thermostated chamber and maintained in the dark at 25 ± 1 °C. The tubes were shaken for one hour, and were standing overnight in the chamber.

The tubes were centrifuged at 25 °C for 10 min at 3500 rpm and sampled. 20.0 ml of the n-octanol phase was transferred to another tube, and shaken with 2.0 ml of n-octanol saturated water for 20 min. The tubes were centrifuged for 10 min at 3500 rpm, samples were taken from the water phase and designated as the n-octanol phase samples. After removal of the n-octanol from the initial samples, the water phase (lower layer) of each replicate of the test article was delivered into a HPLC vial. n-Octanol and water blanks were treated in the same way as the samples. Samples were analysed by HPLC according to the methodology presented in Analytical Conditions

10.5 Results

Nominal concentrations of approximate 0.001 M and 0.0001 M in n-octanol saturated water were selected for partitioning testing. The concentration of Iopamidol measured in each replicate n-octanol or aqueous phase in the partitioning study is presented in Table 11, page 27.

The partition coefficient, P_{ow} , values for Iopamidol determined at concentrations of 9.94×10^{-4} M and 9.94×10^{-5} M were 4.47×10^{-4} and 3.80×10^{-4} , respectively with corresponding $\log P_{ow}$ values of -3.35 and -3.42. Each mean P_{ow} represents the average of three values obtained at each concentration. Iopamidol was shown to partition slightly into the n-octanol phase. Mass balance values (% recovery) ranged from 98.5 % to 105.2 %, and are presented in Table 12, page 27. The temperature inside the thermostated chamber was 25.4 °C during partitioning testing.

10.6 Conclusions

Based on the test results, Iopamidol will not bioaccumulate or sorb onto organic particles. The octanol/water partition coefficient is outside the range of the test method, and should be presented as $\log P_{ow} < 1$.

11. Iopromid

11.1 Description of the test article

-Iopromid, lab code B166/7

Empirical formula: $C_{18}H_{24}I_3N_3O_8$

Molecular weight: 791.12

Physical appearance: White powder

J. Nr: 1104/23-1

11.2 Analytical Conditions

Instrument: Waters HPLC with a Waters 490 Programmable Multiwavelength Detector.

Column: Waters C-18 Novapack 3.9 x 150 mm

Temperature: 25 °C

Flow: 0.7 ml/min

Detector: 254 nm, 0.05 AUFS

Mobile Phase: Acetonitrile/water 3.6:96.4 (v/v)

11.3 Test solution preparation

11.3.1 Stock solution.

A stock solution was prepared for preliminary testing by adding 194.86 mg to a 250.0 ml volumetric flask and dissolving and diluting to volume with n-octanol saturated water. This produced a stock solution of 9.85×10^{-4} M.

11.3.2 Test solution.

The stock solution was used as test solution with a concentration of 9.85×10^{-4} M in n-octanol saturated water. 25.0 ml of the stock solution was diluted with n-octanol saturated water to 250.0 ml to prepare a test solution with a concentration of 9.85×10^{-5} M.

11.4 Test Procedure.

The partitioning study was conducted at two nominal concentrations: approximate 0.001 M and 0.0001M in n-octanol saturated water. Triplicate test systems were prepared in 125 ml centrifuge tubes by equilibrating 50.0 ml water containing Iopromid with 25.0 ml n-octanol. The centrifuge tubes were sealed, shaken vigorously and placed on a shaking table at approximate 150 rpm in a thermostated chamber and maintained in the dark at 25 ± 1 °C. The tubes were shaken for one hour, and were standing overnight in the chamber.

The tubes were centrifuged at 25 °C for 10 min at 3500 rpm and sampled. 20.0 ml of the n-octanol phase was transferred to another tube, and shaken with 2.0 ml of n-octanol saturated water for 20 min. The tubes were centrifuged for 10 min at 3500 rpm, samples were taken from the water phase and designated as the n-octanol phase samples. After removal of the n-octanol from the initial samples, the water phase (lower layer) of each replicate of the test article was delivered into a HPLC vial. n-Octanol and water blanks were treated in the same way as the samples. Samples were analysed by HPLC according to the methodology presented in Analytical Conditions

11.5 Results

Nominal concentrations of approximate 0.001 M and 0.0001 M in n-octanol saturated water were selected for partitioning testing. The concentration of Iopromid measured in each replicate n-octanol or aqueous phase in the partitioning study is presented in Table 13, page 28.

The partition coefficient, P_{ow} , values for Iopromid determined at concentrations of 9.94×10^{-4} M and 9.94×10^{-5} M were 4.47×10^{-4} and 3.80×10^{-4} , respectively with corresponding $\log P_{ow}$ values of -3.35 and -3.42. Each mean P_{ow} represents the average of three values obtained at each concentration. Iopromid was shown to partition slightly into the n-octanol phase. Mass balance values (% recovery) ranged from 98.5 % to 105.2 %, and are presented in Table 14, page 28. The temperature inside the thermostated chamber ranged from 25.3 to 25.4 °C during partitioning testing.

11.6 Conclusions

Based on the test results, Iopromid will not bioaccumulate or sorb onto organic particles. The octanol/water partition coefficient is outside the range of the test method, and should be presented as $\log P_{ow} < 1$.

12. Deviations from the FDA description of the test.

The preliminary equilibration test, as described in the FDA method, was not carried out. As the test chemicals were allowed to equilibrate between n-octanol and water over night, omitting the preliminary test is not believed to affect the outcome of the study.

References:

Leo, H., Hansch, C. and Elkins, D.; "Partition Coefficient and Their Uses.", *Chemical Reviews*, 71, (6), 1971.

U.S. Food and Drug Administration, Environmental Assessment Technical Assistance Handbook section 3.02; n-Octanol/Water Partition Coefficient, March 1987.

OECD (Organisation for Economic Co-operation and Development) 1981. Partition Coefficient (n-octanol/water), Flask Shaking Method, Method 107. In OECD Guidelines for Testing of Chemicals. Paris, France.

Table 1 Calculations of the partition coefficient for Iodixanol

Nominal concentration [M]	Concentration in n-octanol [M]	Concentration in water [M]	Calculated P_{ow}	$\log P_{ow}$
1,00E-3	5,59E-07	9,17E-04	6,09E-04	-3,22
1,00E-3	3,68E-07	9,31E-04	3,96E-04	-3,40
1,00E-3	4,68E-07	9,23E-04	5,07E-04	-3,29
1,00E-4	1,05E-07	9,83E-05	1,06E-03	-2,97
1,00E-4	3,10E-08	9,84E-05	3,15E-04	-3,50
1,00E-4	1,42E-08	9,85E-05	1,44E-04	-3,84

Calculated mean 1,00E-3 M solution: $-3,30 \pm 0,09$

Calculated mean 1,00E-4M solution: $-3,44 \pm 0,44$

Table 2 Calculations of the recovery for Iodixanol

Expected [mg]	Found [mg]	% Recovery
77,53	71,08	91,69
77,53	72,20	93,13
77,53	71,55	92,29
7,75	7,63	98,36
7,75	7,63	98,36
7,75	7,63	98,46

Table 3 Calculations of the partition coefficient for Iotrolan

Nominal concentration [M]	Concentration in n-octanol [M]	Concentration in water [M]	Calculated P_{ow}	$\log P_{ow}$
9,95E-4	6,16E-07	9,44E-04	6,53E-04	-3,19
9,95E-4	2,21E-08	9,48E-04	2,33E-05	-4,63
9,95E-4	1,48E-08	9,65E-04	1,53E-05	-4,82
9,95E-5	7,38E-09	1,02E-04	7,26E-05	-4,14
9,95E-5	6,15E-09	1,01E-04	6,09E-05	-4,22
9,95E-5	4,92E-09	1,01E-04	4,88E-05	-4,31

Calculated mean 9,95E-4 M solution: $-4,21 \pm 0,89$

Calculated mean 9,95E-5 M solution: $-4,22 \pm 0,09$

Table 4 Calculations of the recovery for Iotrolan

Expected [mg]	Found [mg]	% Recovery
80,94	76,75	94,82
80,94	77,12	95,27
80,94	78,44	96,91
4,05	4,13	102,11
4,05	4,11	101,45
4,05	4,10	101,38

Table 5 Calculations of the partition coefficient for Iohexol

Nominal concentration [M]	Concentration in n-octanol [M]	Concentration in water [M]	Calculated P _{ow}	log P _{ow}
9,95E-4	5,98E-07	8,74E-04	6,84E-04	-3,16
9,95E-4	5,20E-07	8,75E-04	5,94E-04	-3,23
9,95E-4	5,85E-07	8,76E-04	6,67E-04	-3,18
9,95E-5	2,56E-08	7,58E-05	3,37E-04	-3,47
9,95E-5	4,99E-08	7,60E-05	6,57E-04	-3,18
9,95E-5	2,80E-08	7,58E-05	3,70E-04	-3,43

Calculated mean 9,95E-4 M solution: $-3,19 \pm 0,03$

Calculated mean 9,95E-5 M solution: $-3,36 \pm 0,16$

Table 6 Calculations of the recovery for Iohexol

Expected [mg]	Found [mg]	% Recovery
40,85	35,88	87,82
40,85	35,95	87,98
40,85	35,99	88,08
4,09	3,11	76,23
4,09	3,12	76,42
4,09	3,11	76,18

Table 7 Calculations of the partition coefficient for Iopentol

Nominal concentration [M]	Concentration in n-octanol [M]	Concentration in water [M]	Calculated P_{ow}	$\log P_{ow}$
9,88E-4	4,75E-07	9,49E-04	5,01E-04	-3,30
9,88E-4	3,41E-07	9,46E-04	3,61E-04	-3,44
9,88E-4	4,26E-07	9,51E-04	4,48E-04	-3,35
9,88E-5	1,80E-08	1,03E-04	1,75E-04	-3,76
9,88E-5	4,67E-08	1,03E-04	4,55E-04	-3,34
9,88E-5	2,63E-08	1,03E-04	2,57E-04	-3,59

Calculated mean 9,88E-4 M solution: $-3,36 \pm 0,07$

Calculated mean 9,88E-5 M solution: $-3,56 \pm 0,21$

Table 8 Calculations of the recovery for Iopentol

Expected [mg]	Found [mg]	% Recovery
41,20	39,65	96,24
41,20	39,49	95,85
41,20	39,74	96,45
4,12	4,29	104,02
4,12	4,28	103,98
4,12	4,29	104,06

Table 9 Calculations of the partition coefficient for Ioversol

Nominal concentration [M]	Concentration in n-octanol [M]	Concentration in water [M]	Calculated P_{ow}	$\log P_{ow}$
1,01E-3	1,10E-07	9,48E-04	1,16E-04	-3,93
1,01E-3	2,53E-07	9,37E-04	2,70E-04	-3,57
1,01E-3	2,49E-07	9,47E-04	2,63E-04	-3,58
1,01E-4	1,12E-08	1,01E-04	1,11E-04	-3,96
1,01E-4	1,24E-08	1,01E-04	1,23E-04	-3,91
1,01E-4	1,24E-08	1,01E-04	1,22E-04	-3,91

Calculated mean 1,01E-3 M solution: $-3,69 \pm 0,21$

Calculated mean 1,01E-4 M solution: $-3,93 \pm 0,03$

Table 10 Calculations of the recovery for Ioversol

Expected [mg]	Found [mg]	% Recovery
40,64	38,25	94,11
40,64	37,81	93,02
40,64	38,23	94,06
4,06	4,07	100,07
4,06	4,08	100,31
4,06	4,10	100,78

Table 11 Calculations of the partition coefficient for Iopamidol

Nominal concentration [M]	Concentration in n-octanol [M]	Concentration in water [M]	Calculated P_{ow}	$\log P_{ow}$
9,94E-4	4,45E-07	9,78E-04	4,55E-04	-3,34
9,94E-4	4,76E-07	9,82E-04	4,85E-04	-3,31
9,94E-4	4,08E-07	9,80E-04	4,16E-04	-3,38
9,94E-5	3,99E-08	1,04E-04	3,84E-04	-3,42
9,94E-5	5,02E-08	1,04E-04	4,80E-04	-3,32
9,94E-5	3,09E-08	1,04E-04	2,97E-04	-3,53

Calculated mean 9,94E-4 M solution: $-3,35 \pm 0,03$

Calculated mean 9,94E-5 M solution: $-3,42 \pm 0,10$

Table 12 Calculations of the recovery for Iopamidol

Expected [mg]	Found [mg]	% Recovery
15,45	15,21	98,45
15,45	15,28	98,86
15,45	15,24	98,65
1,55	1,62	104,68
1,55	1,63	105,17
1,55	1,62	104,69

Table 13 Calculations of the partition coefficient for Iopromid

Nominal concentration [M]	Concentration in n-octanol [M]	Concentration in water [M]	Calculated P_{ow}	$\log P_{ow}$
9,85E-4	2,87E-07	9,16E-04	3,13E-04	-3,50
9,85E-4	3,89E-07	9,41E-04	4,14E-04	-3,38
9,85E-4	1,98E-07	9,33E-04	2,13E-04	-3,67
9,85E-5	4,04E-08	9,93E-05	4,07E-04	-3,39
9,85E-5	6,45E-08	9,93E-05	6,49E-04	-3,19
9,85E-5	4,42E-08	9,95E-05	4,45E-04	-3,35

Calculated mean 9,85E-4 M solution: $-3,52 \pm 0,15$

Calculated mean 9,85E-5 M solution: $-3,31 \pm 0,11$

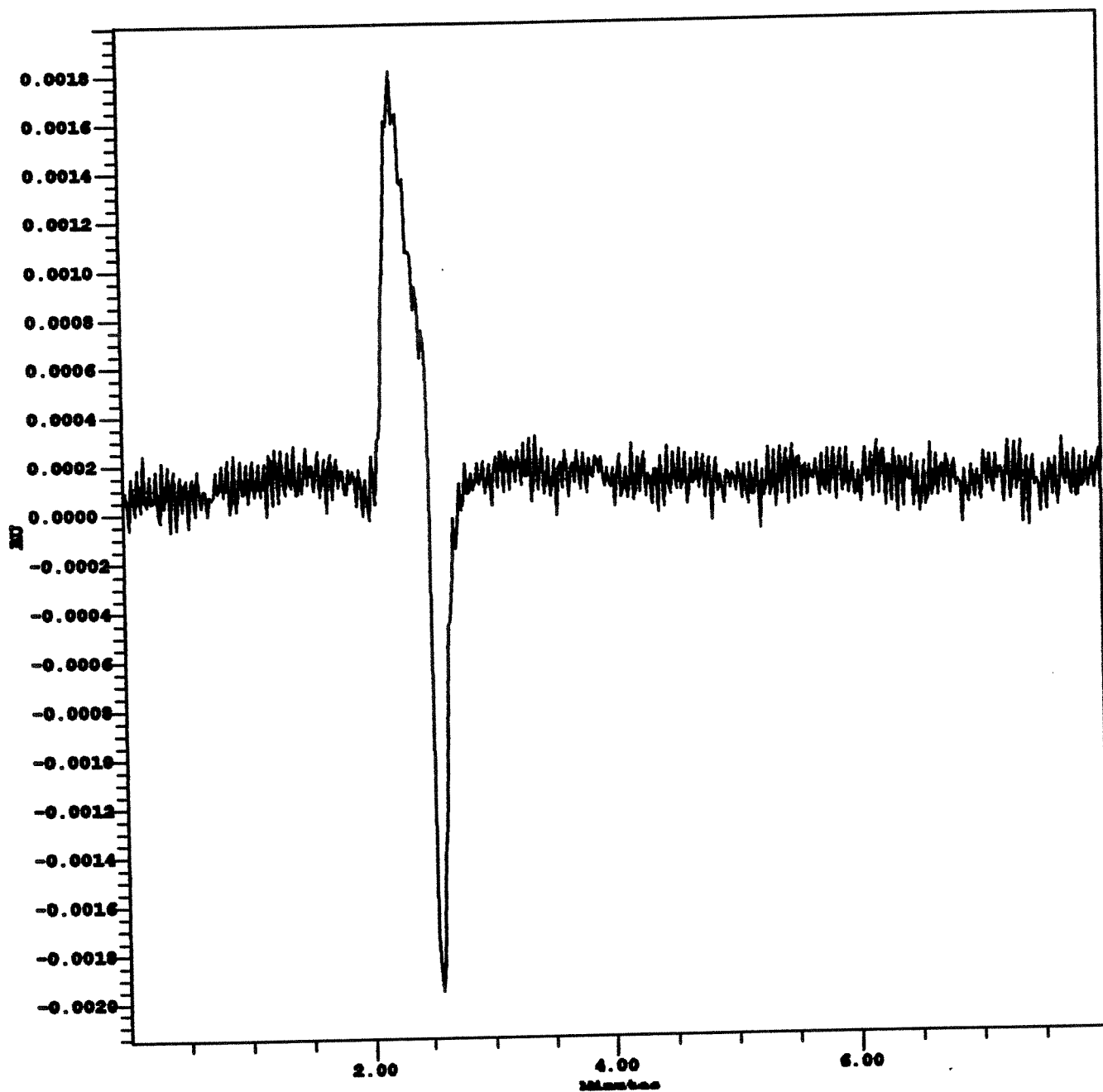
Table 14 Calculations of the recovery for Iopromid

Expected [mg]	Found [mg]	% Recovery
15,59	14,49	92,98
15,59	14,90	95,55
15,59	14,77	94,77
1,56	1,57	100,82
1,56	1,57	100,89
1,56	1,57	101,03

Chromatogram of the water phase of a blank sample

Millennium Sample Information

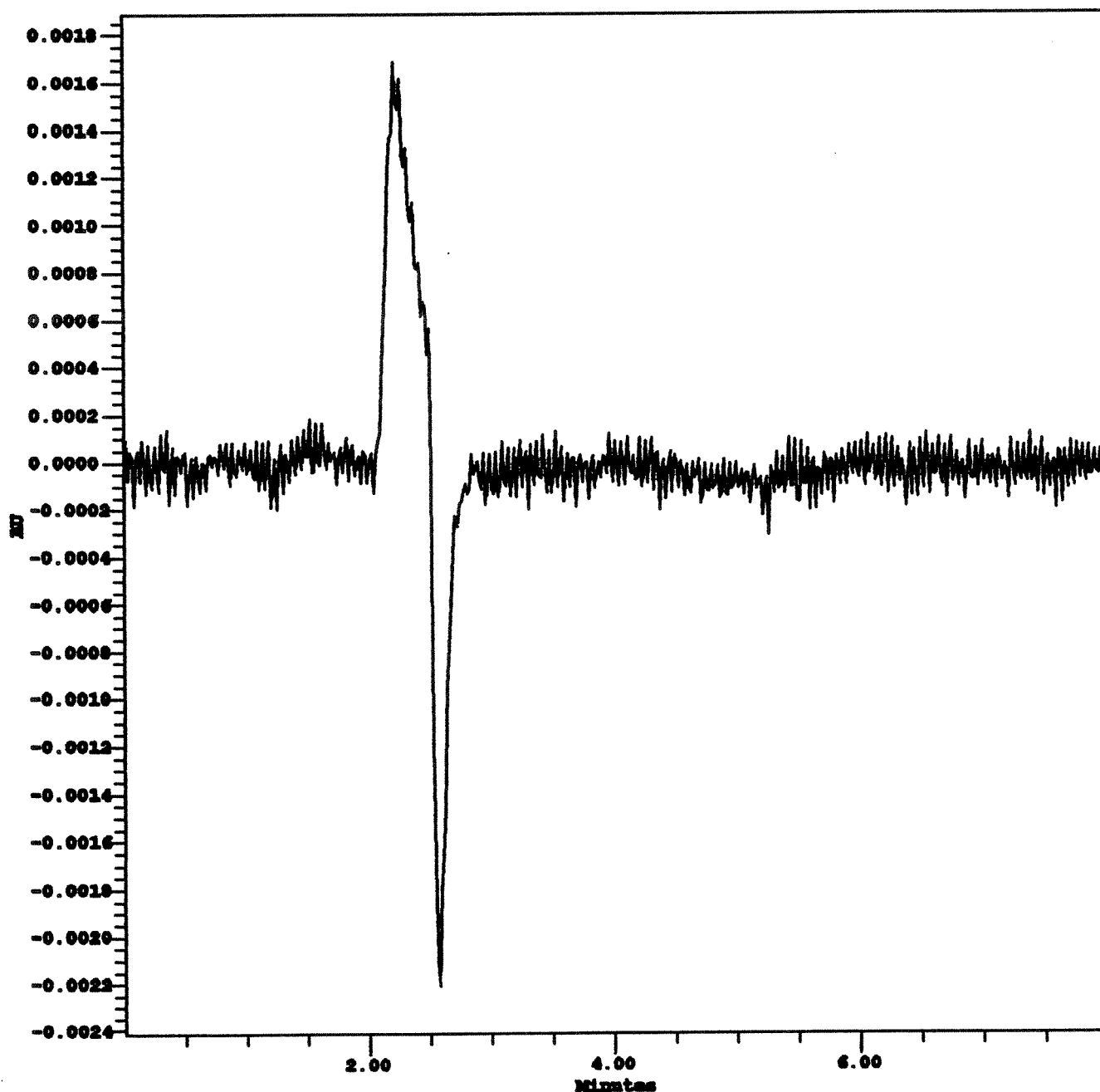
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Sample Name:	BL V.FASE	Volume:	150.00 <i>ul</i>
Vial:	61	Run Time:	8.0 min
Injection:	1	Date Processed:	11/01/95 15:53
Channel:	490 Ch1	Dilution:	1.00000
Date Acquired:	11/01/95 15:44		
Scale Factor:	1.00		
Acq Meth Set:	ioversol		
Processing Method:	ioversol1		
Username	tos_niva		



Chromatogram of the n-octanol phase of a blank sample

Millennium Sample Information

Project Name:	div	Sample Type:	Unknown
Sample Name:	BL O.FASE	Volume:	150.00 μ l
Vial:	62	Run Time:	8.0 min
Injection:	1	Date Processed:	11/01/95 16:03
Channel:	490 Ch1	Dilution:	1.00000
Date Acquired:	11/01/95 15:54		
Scale Factor:	12.50		
Acq Meth Set:	ioversol		
Processing Method:	ioversol1		
Username	tos_niva		

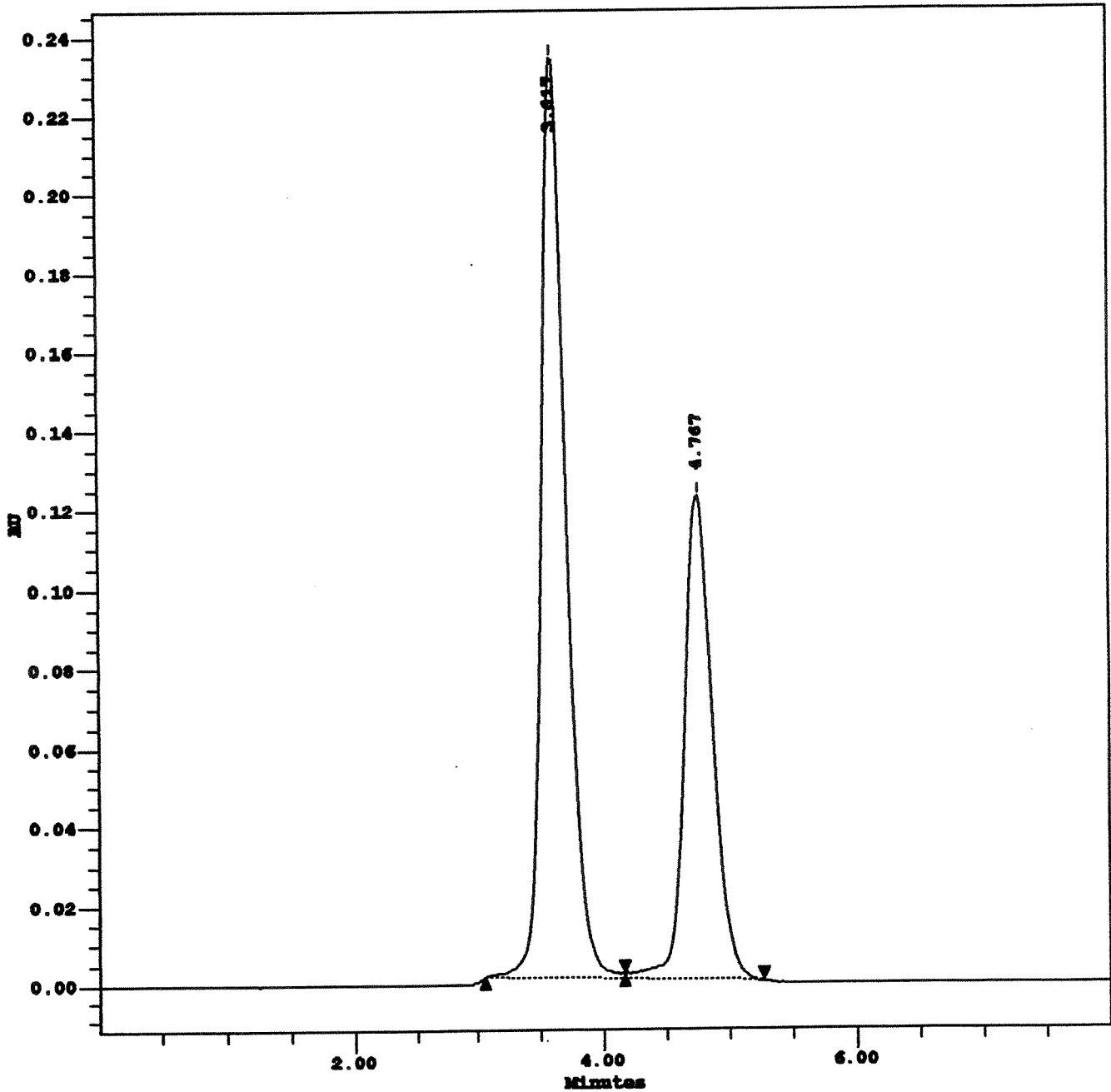


Chromatogram of the water phase of a Iodixanol sample

Millennium Sample Information

Project Name: div
Sample Name: b166/1 0.001Mv
Vial: 10
Injection: 1
Channel: 490 Ch1
Date Acquired: 04/01/95 13:44
Scale Factor: 1.00
Acq Meth Set: div_set
Processing Method: iodixanol
Username tos_niva

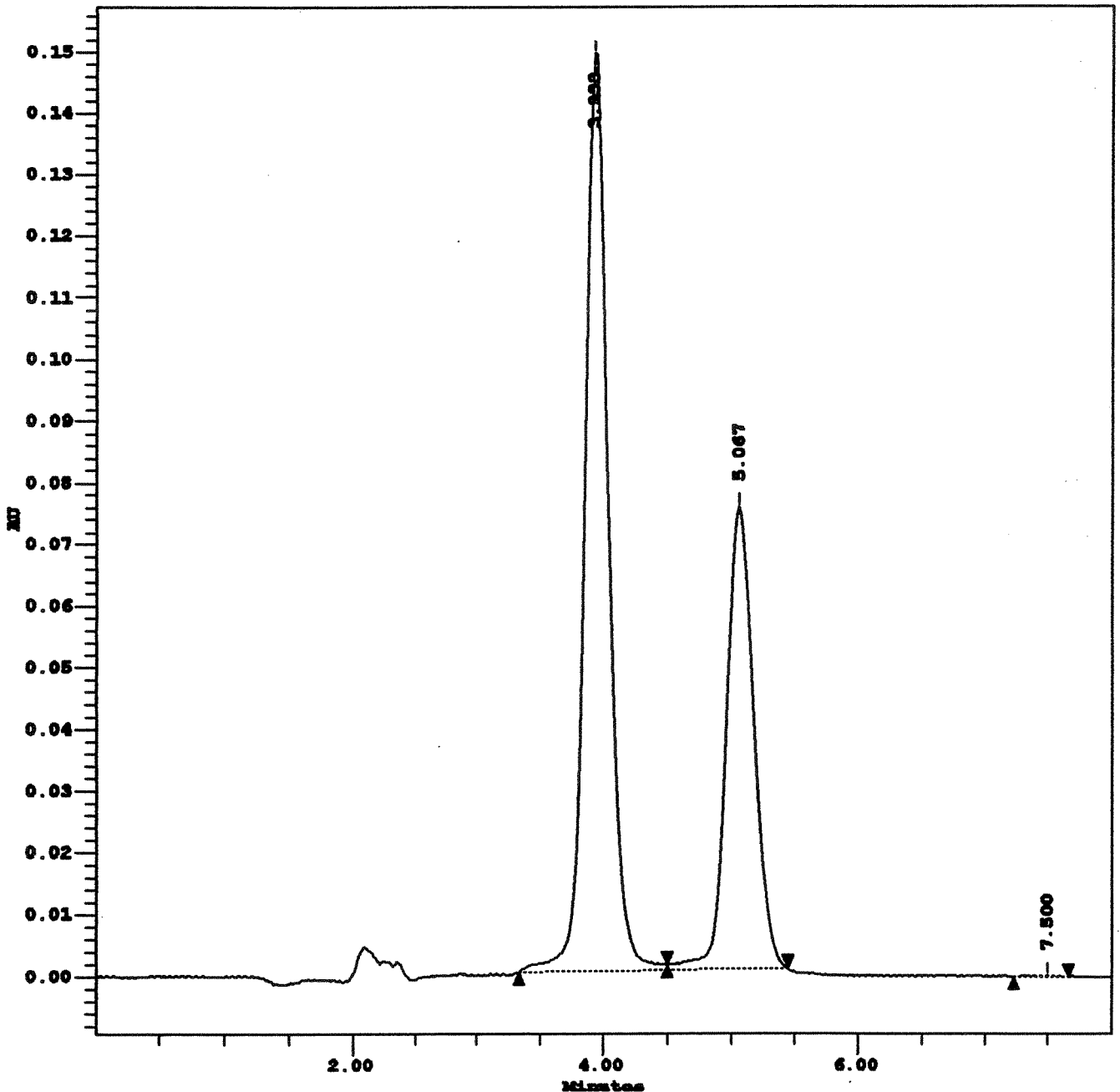
Sample Type: Unknown
Volume: 1.50 μ l
Run Time: 8.0 min
Date Processed: 12/01/95 09:35
Dilution: 100.00000



Chromatogram of the n-octanol phase of a Iodixanol sample

Millennium Sample Information

Project Name:	div	Sample Type:	Unknown
Sample Name:	b166/1 0.001Mo	Volume:	150.00 μ l
Vial:	9	Run Time:	8.0 min
Injection:	1	Date Processed:	12/01/95 09:30
Channel:	490 Ch1	Dilution:	1.00000
Date Acquired:	04/01/95 13:31		
Scale Factor:	10.00		
Acq Meth Set:	div_set		
Processing Method:	iodixanol		
Username	tos_niva		

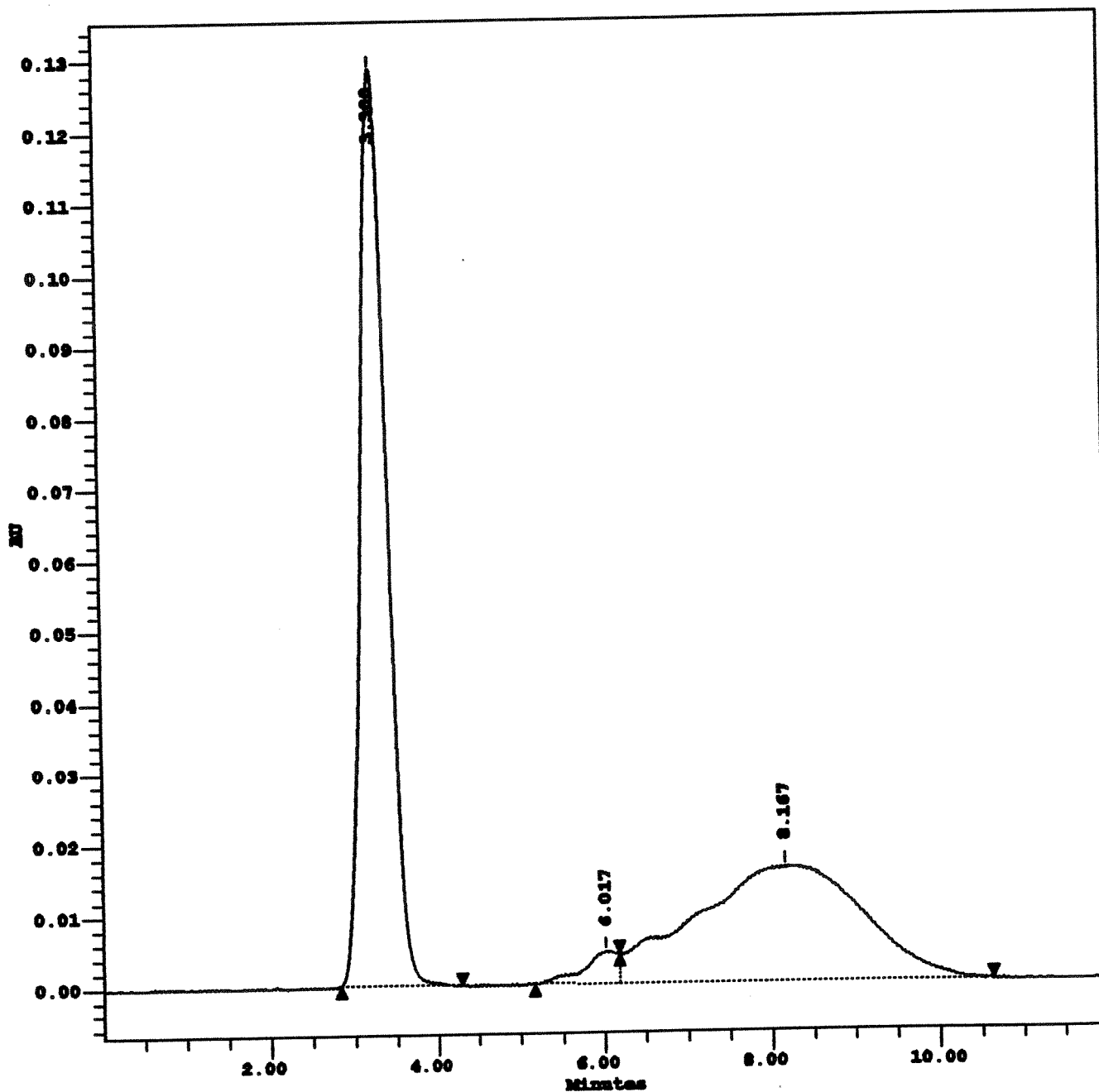


Chromatogram of the water phase of a Iotrolan sample

Millennium Sample Information

Project Name: div
Sample Name: b166/2 hoyv1
Vial: 23
Injection: 1
Channel: 490 Ch1
Date Acquired: 08/01/95 17:00
Scale Factor: 1.00
Acq Meth Set: iotrolan
Processing Method: iotrolan
Username: tos_niva

Sample Type: Unknown
Volume: 1.50 μ l
Run Time: 12.0 min
Date Processed: 09/01/95 07:51
Dilution: 100.00000

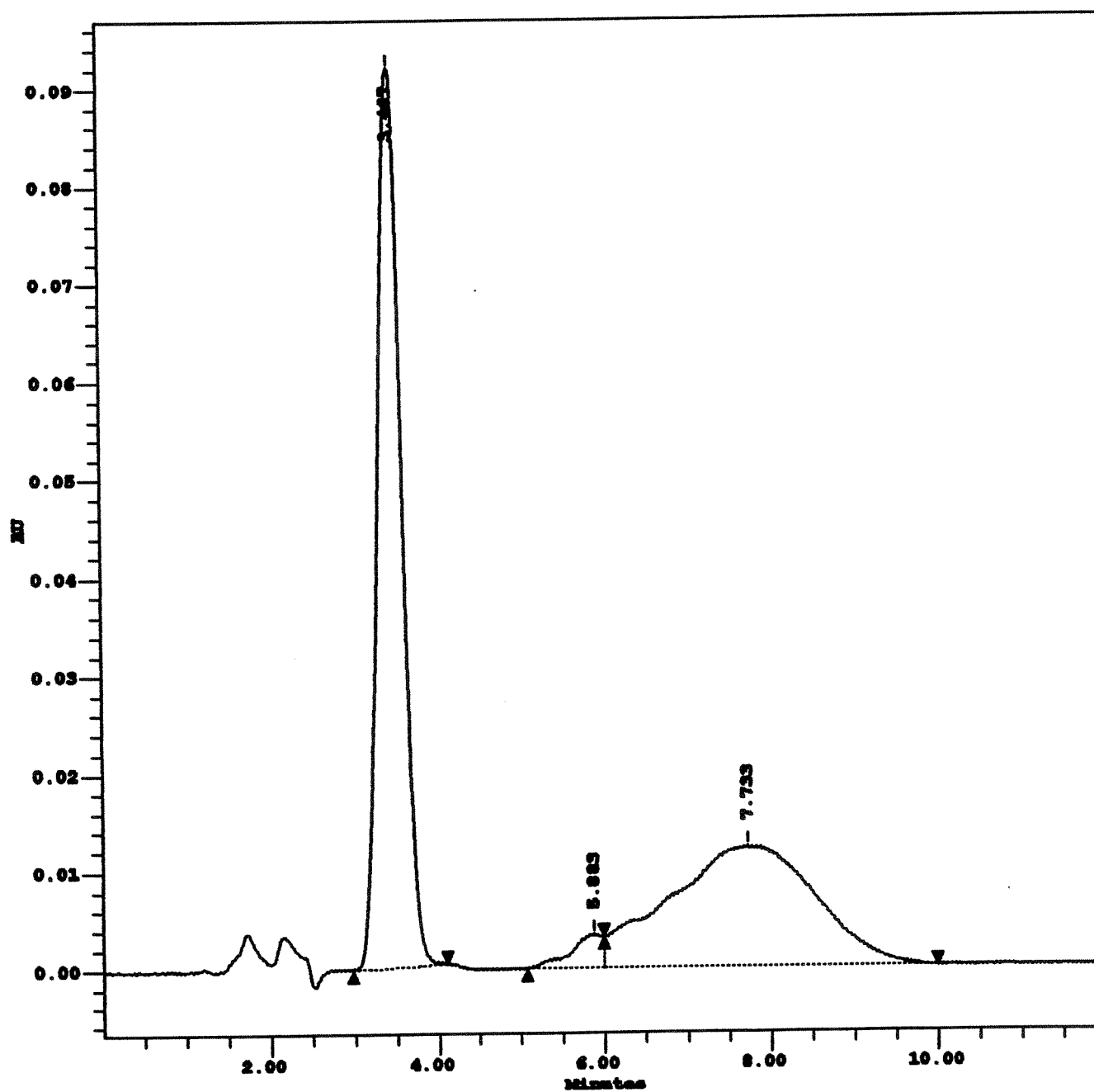


Chromatogram of the n-octanol phase of a Iotrolan sample

Millennium Sample Information

Project Name: div
Sample Name: b166/2 HOYO1
Vial: 24
Injection: 1
Channel: 490 Ch1
Date Acquired: 06/01/95 12:51
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Acq Meth Set: iotrolan
Processing Method: iotrolan
Username: tos_niva

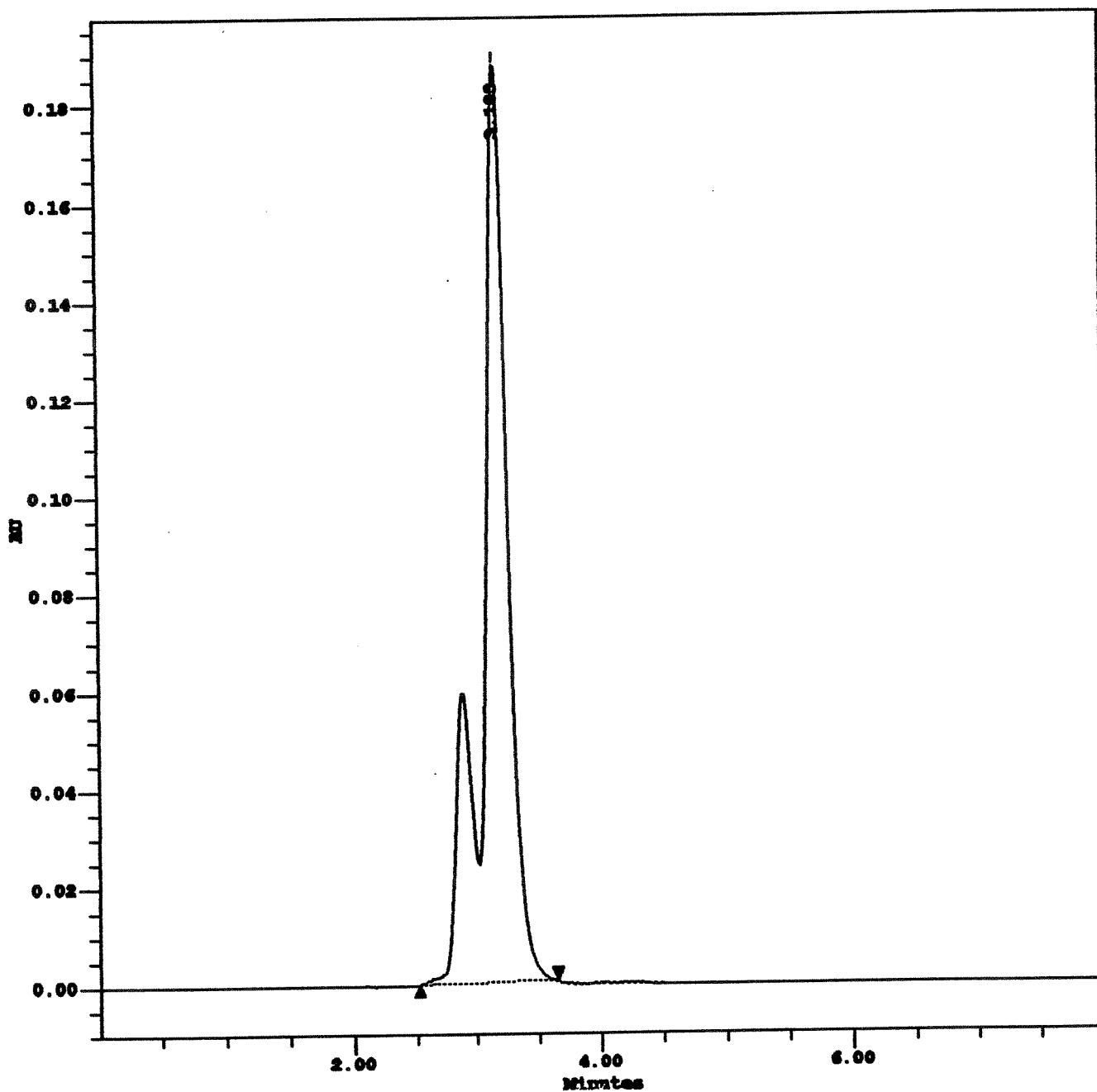
Sample Type: Unknown
Volume: 150.00 μ l
Run Time: 12.0 min
Date Processed: 09/01/95 07:53
Dilution: 1.00000



Chromatogram of the water phase of a Iohexol sample

Millennium Sample Information

Project Name:	div	Sample Type:	Unknown
Sample Name:	b166/3 HOYV1	Volume:	1.50 μ l
Vial:	11	Run Time:	8.0 min
Injection:	1	Date Processed:	09/01/95 12:54
Channel:	490 Ch1	Dilution:	100.00000
Date Acquired:	06/01/95 14:21		
Scale Factor:	1.00		
Acq Meth Set:	iohexol		
Processing Method:	iohexol1		
Username:	tos_niva		

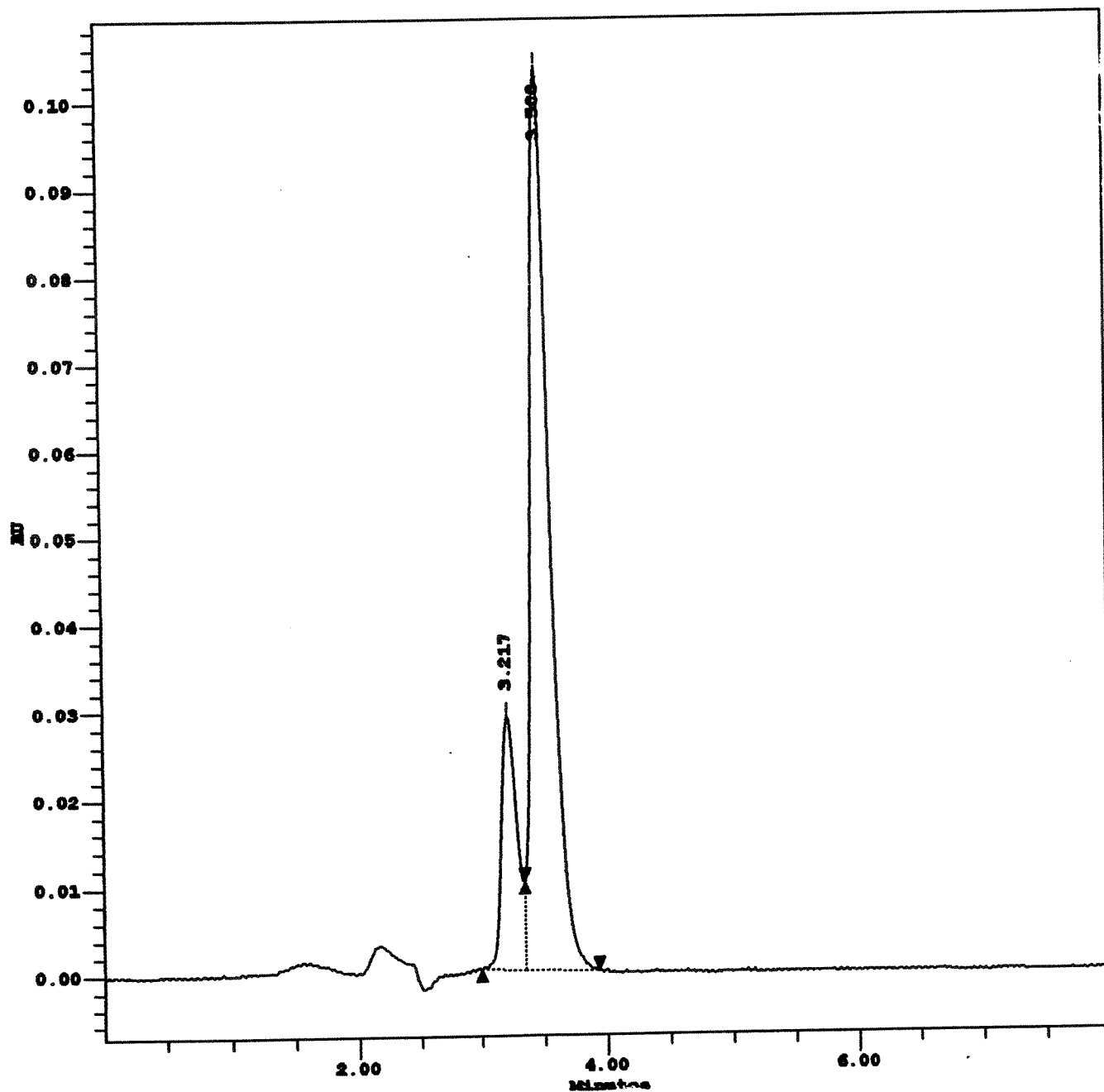


Chromatogram of the n-octanol phase of a Iohexol sample

Millennium Sample Information

Project Name: div
Sample Name: b166/3 HOY01
Vial: 12
Injection: 1
Channel: 490 Ch1
Date Acquired: 06/01/95 10:22
Scale Factor: 7.50
Acq Meth Set: iohexol
Processing Method: iohexol1
Username: tos_niva

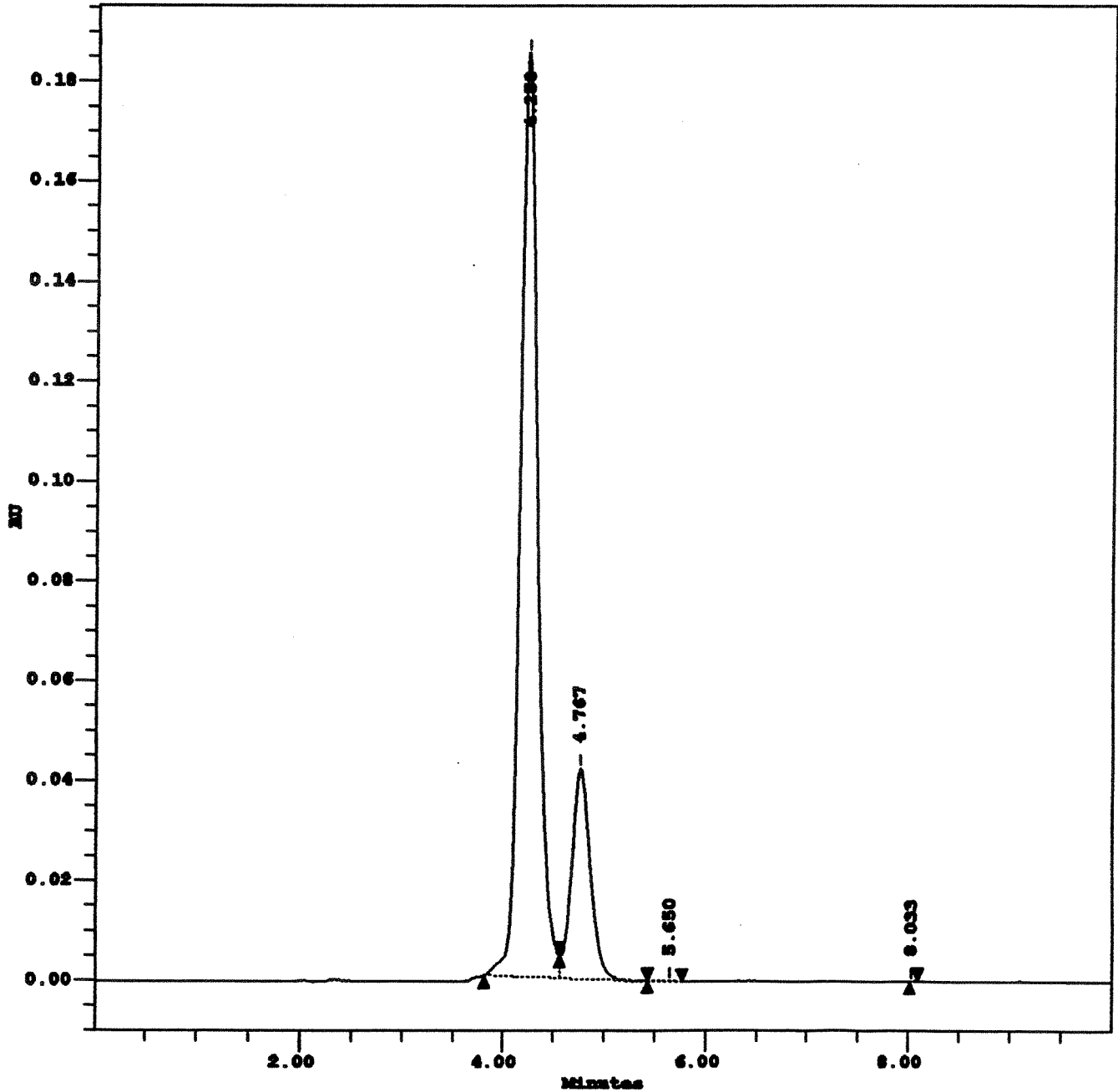
Sample Type: Unknown
Volume: 150.00 μ l
Run Time: 8.0 min
Date Processed: 09/01/95 16:00
Dilution: 1.00000



Chromatogram of the water phase of a Iopentol sample

Millennium Sample Information

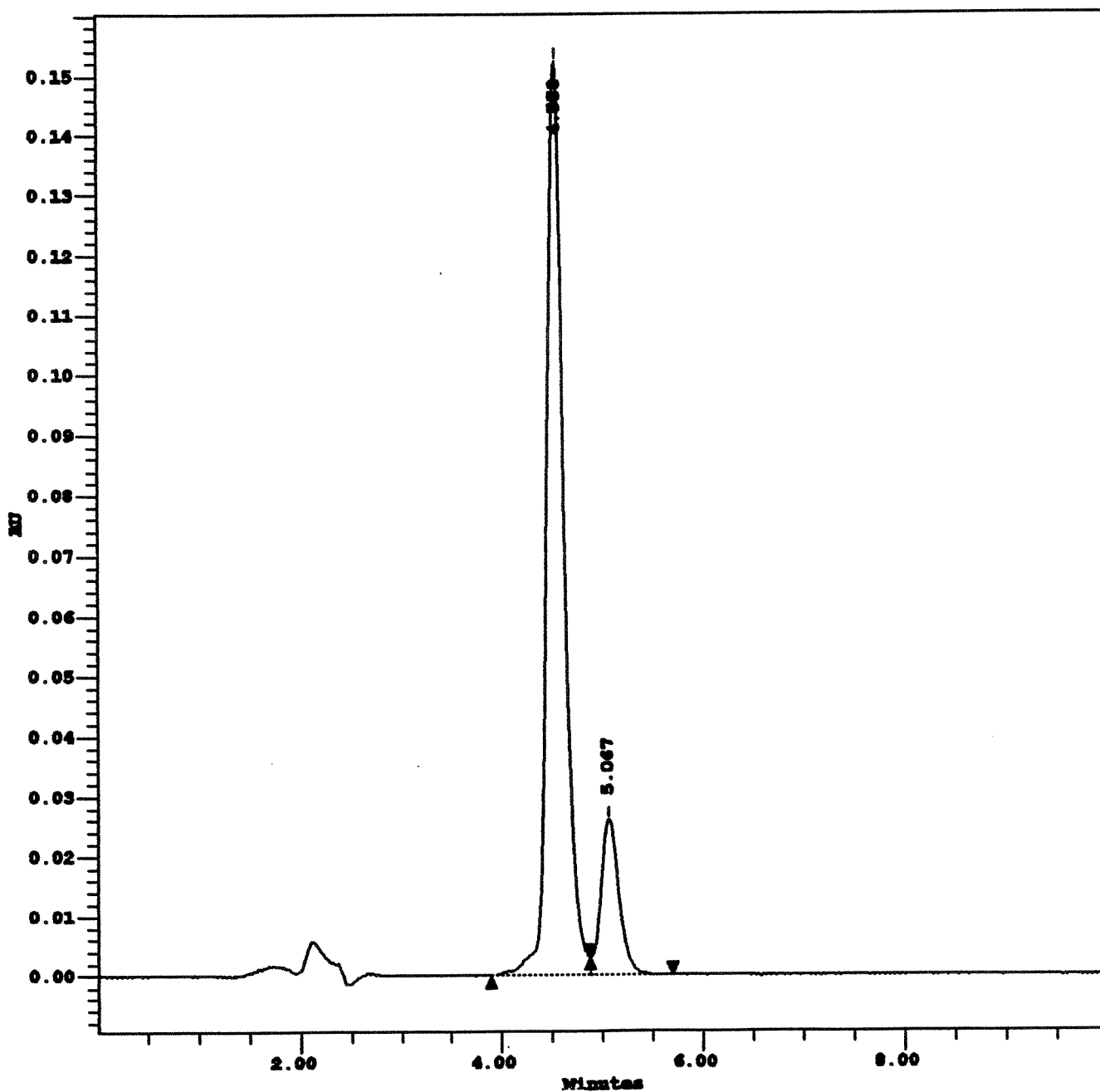
Project Name:	div	Sample Type:	Unknown
Sample Name:	b166/4 hoyv1	Volume:	1.50 μ l
Vial:	49	Run Time:	10.0 min
Injection:	1	Date Processed:	09/01/95 13:04
Channel:	490 Ch1	Dilution:	100.00000
Date Acquired:	09/01/95 12:39		
Scale Factor:	1.00		
Acq Meth Set:	iopentol		
Processing Method:	iopentol		
Username:	tos_niva		



Chromatogram of the n-octanol phase of a Iopentol sample

Millennium Sample Information

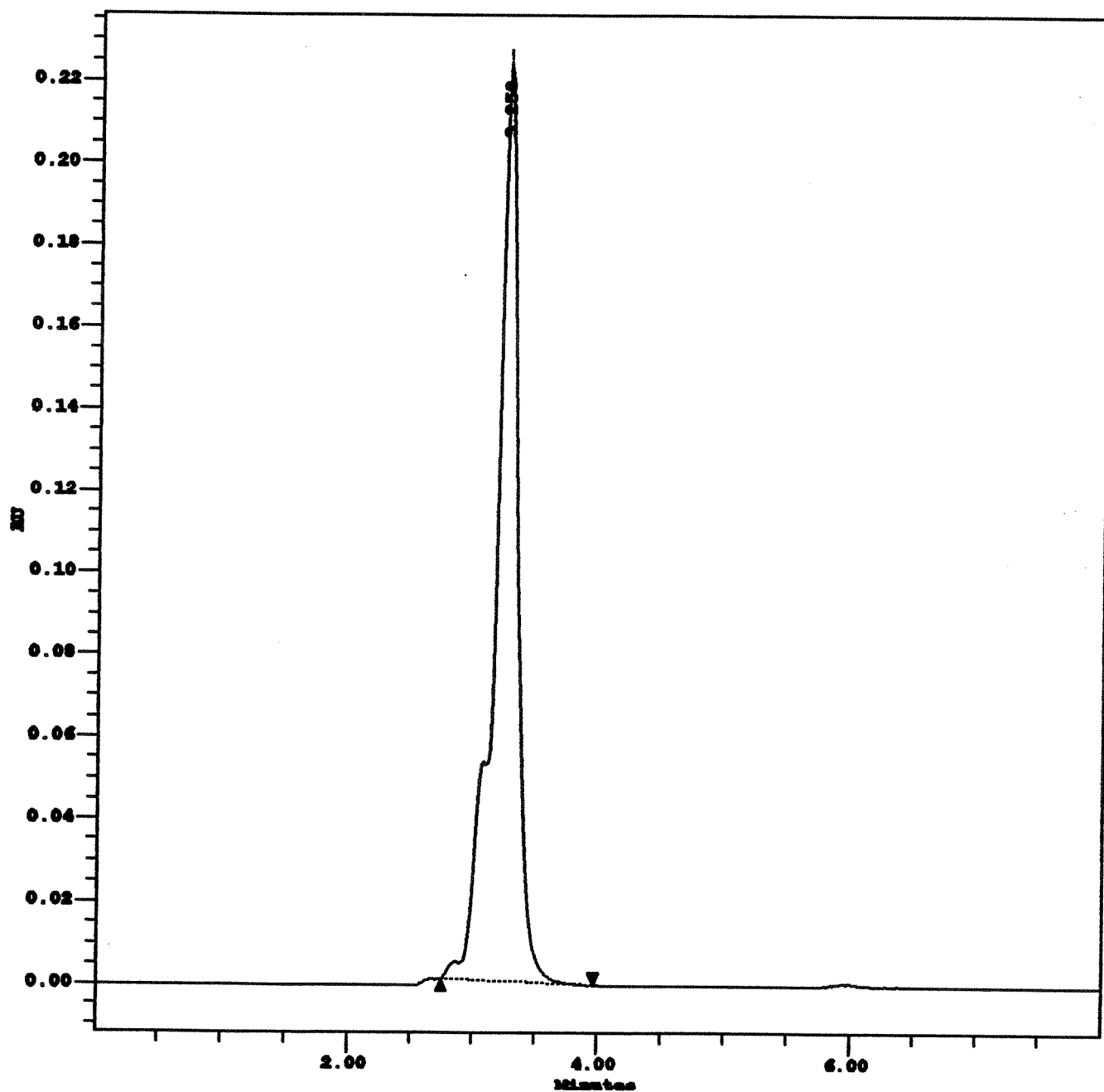
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Sample Name:	b166/4 hoyo1	Volume:	150.00 μ l
Vial:	52	Run Time:	10.0 min
Injection:	1	Date Processed:	09/01/95 15:50
Channel:	490 Ch1	Dilution:	1.00000
Date Acquired:	09/01/95 13:13		
Scale Factor:	15.00		
Acq Meth Set:	iopentol		
Processing Method:	iopentol		
Username:	tos_niva		



Chromatogram of the water phase of a Ioversol sample

Millennium Sample Information

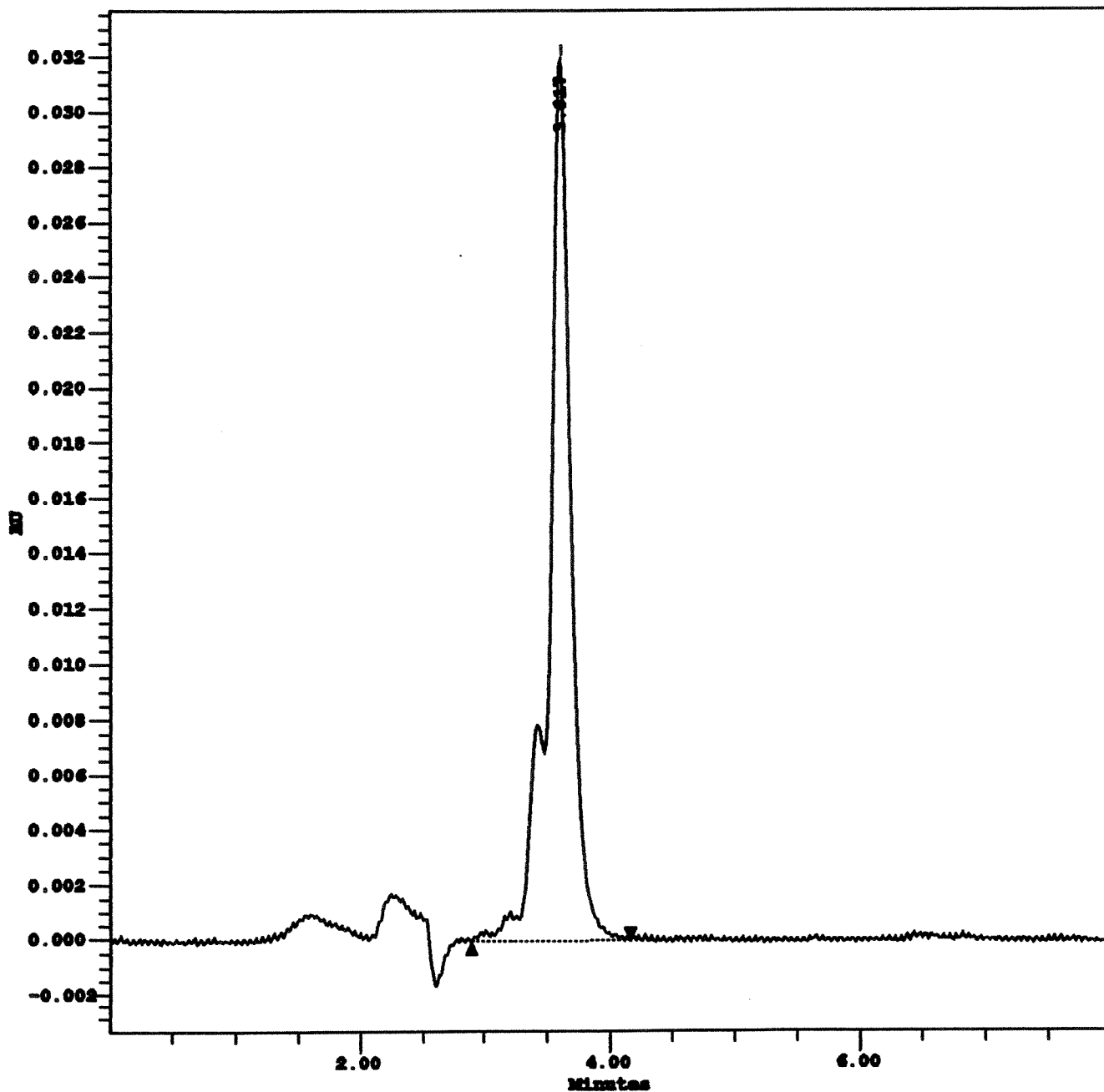
Project Name:	div	Sample Type:	Unknown
Sample Name:	B166/5HOYV1	Volume:	1.50 μ l
Vial:	25	Run Time:	8.0 min
Injection:	1	Date Processed:	11/01/95 14:54
Channel:	490 Ch1	Dilution:	100.00000
Date Acquired:	11/01/95 14:45		
Scale Factor:	1.00		
Acq Meth Set:	ioversol		
Processing Method:	ioversol1		
Username	tos_niva		



Chromatogram of the n-octanol phase of a Ioversol sample

Millennium Sample Information

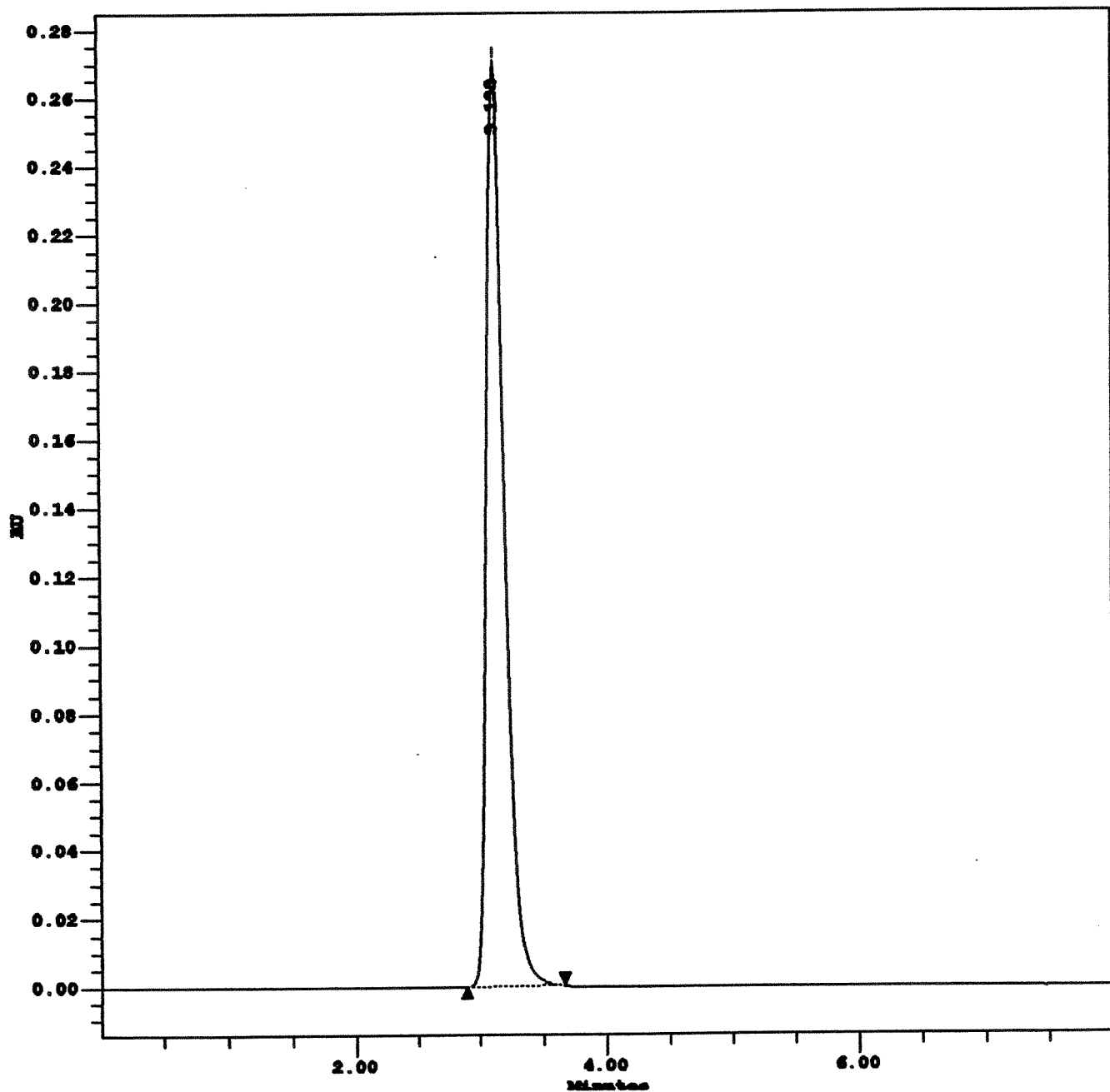
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Sample Name:	B166/5 hoyo1	Volume:	150.00 μ l
Vial:	70	Run Time:	8.0 min
Injection:	1	Date Processed:	10/01/95 13:15
Channel:	490 Ch1	Dilution:	1.00000
Date Acquired:	10/01/95 08:12		
Scale Factor:	12.50		
Acq Meth Set:	ioversol		
Processing Method:	ioversol1		
Username	tos_niva		



Chromatogram of the water phase of a Iopamidol sample

Millennium Sample Information

Project Name:	div	Sample Type:	Unknown
Sample Name:	b166/6 hoyv1	Volume:	1.50 μ l
Vial:	85	Run Time:	8.0 min
Injection:	1	Date Processed:	10/01/95 15:27
Channel:	490 Ch1	Dilution:	100.00000
Date Acquired:	10/01/95 11:51		
Scale Factor:	1.00		
Acq Meth Set:	iopamidol		
Processing Method:	iopamidol		
Username:	tos_niva		

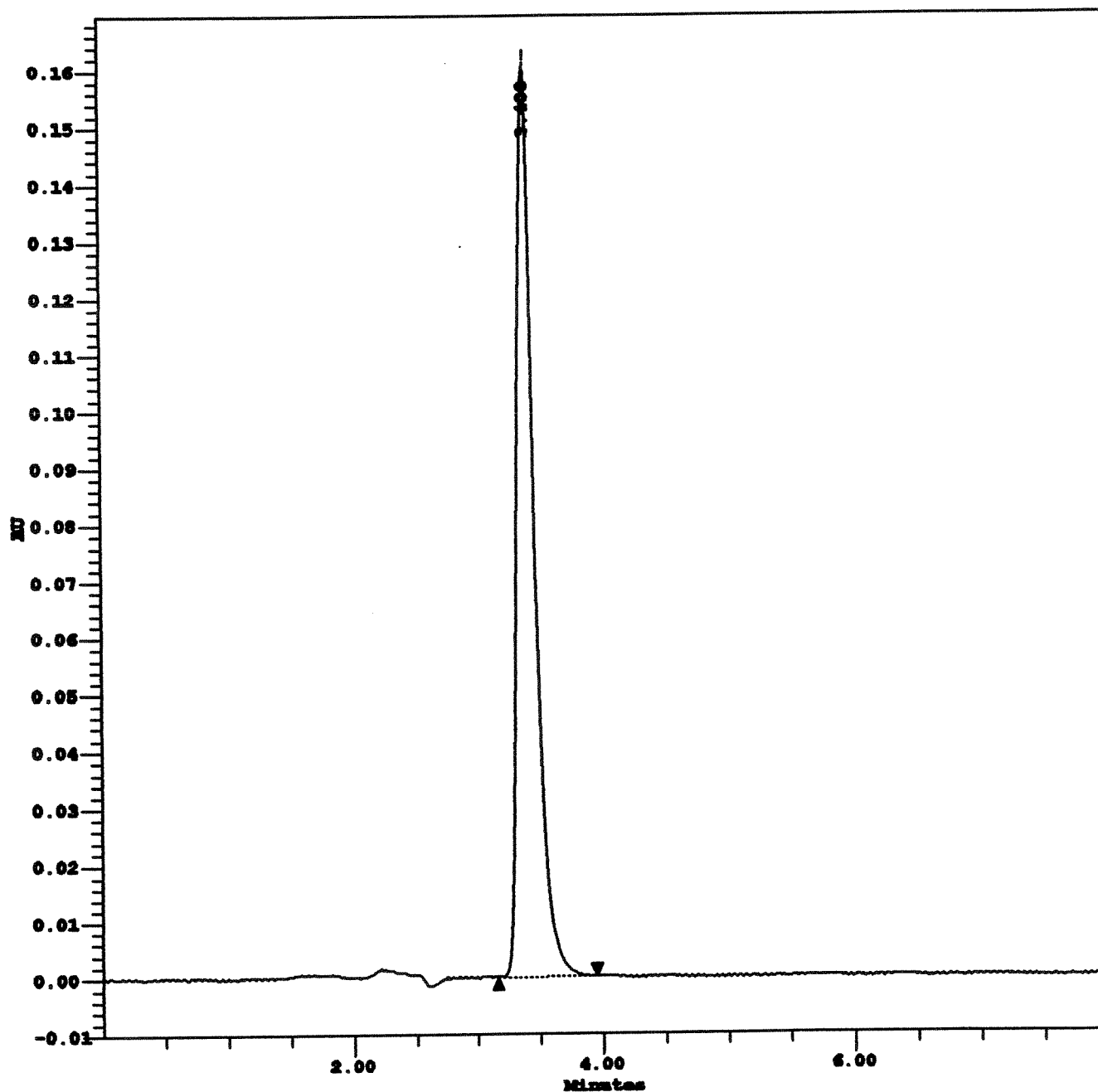


Chromatogram of the n-octanol phase of a Iopamidol sample

Millennium Sample Information

Project Name: div
Sample Name: b166/6 hoyo1
Vial: 88
Injection: 1
Channel: 490 Ch1
Date Acquired: 10/01/95 12:20
Scale Factor: 12.50
Acq Meth Set: iopamidol
Processing Method: iopamidol
Username tos_niva

Sample Type: Unknown
Volume: 150.00 μ l
Run Time: 8.0 min
Date Processed: 10/01/95 15:16
Dilution: 1.00000

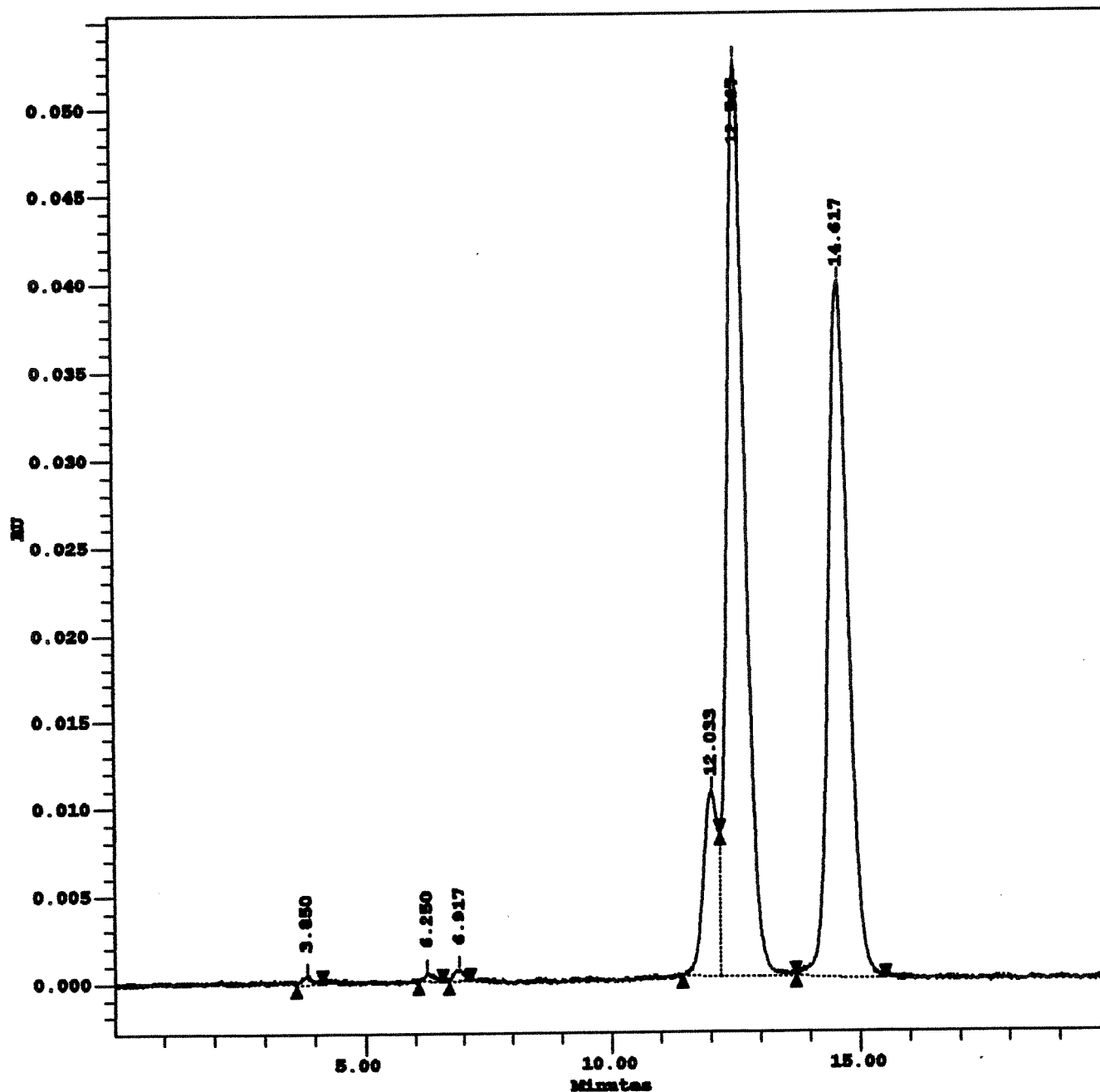


Chromatogram of the water phase of a Iopromid sample

Millennium Sample Information

Project Name: div
Sample Name: b166/7 hoyv1
Vial: 1
Injection: 1
Channel: 490 Ch1
Date Acquired: 10/01/95 17:09
Scale Factor: 1.00
Acq Meth Set: iopromid
Processing Method: iopromid
Username tos_niva

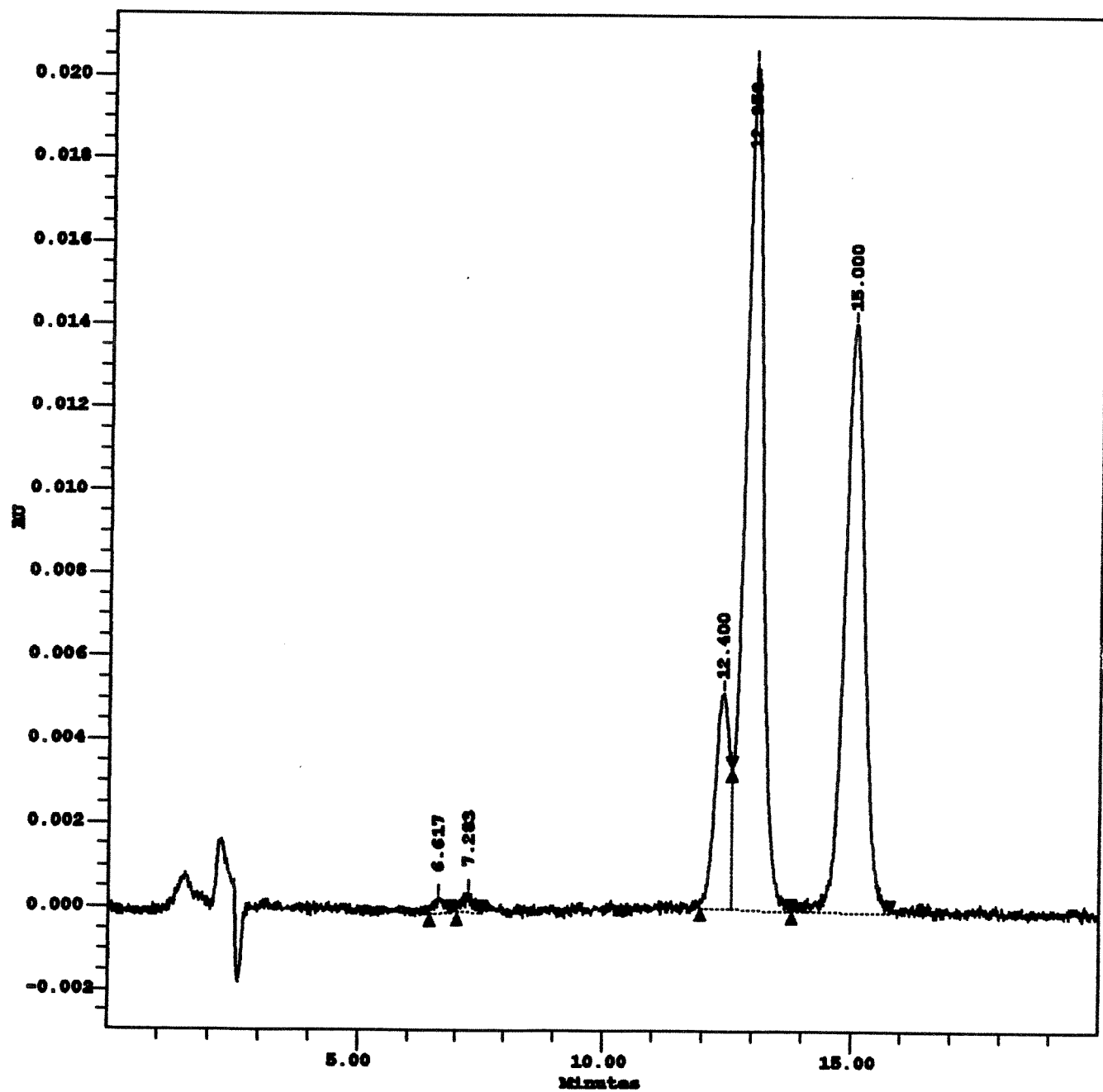
Sample Type: Unknown
Volume: 1.50 μ l
Run Time: 20.0 min
Date Processed: 11/01/95 12:48
Dilution: 100.00000



Chromatogram of the n-octanol phase of a Iopromid sample

Millennium Sample Information

Project Name:	div	Sample Type:	Unknown
Sample Name:	b166/7 hoyo1	Volume:	150.00 μ l
Vial:	4	Run Time:	20.0 min
Injection:	1	Date Processed:	11/01/95 12:45
Channel:	490 Ch1	Dilution:	1.00000
Date Acquired:	10/01/95 18:14		
Scale Factor:	12.50		
Acq Meth Set:	iopromid		
Processing Method:	iopromid		
Username:	tos_niva		



NIVA



Norwegian Institute for Water Research
P.O.Box 173, Kjelsås N-0411 Oslo, Norway
Phone: + 47 22 18 51 00 Fax: + 47 22 18 52 00
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