

Pharmacokinetics of Ifosfamide and metabolites

B. GOURMEL*, **S. DENIS***, **Nicole DELEPINE****

* Laboratoire de Biochimie Hôpital St Louis PARIS

** Service d'Oncologie Pédiatrique

www.nicoledelepine.fr

IFOSFAMIDE (Prodrug)

**Cyt P 450
3 A 4**

2 D IFOS.

+ Chloracetaldehyde

3 D IFOS.

+ Chloracetaldehyde

4 OH IFOS.

CELL

Ifos. Mustard + **Acrolein**

4 OH IFOS.

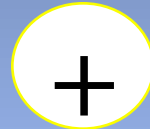
4 Keto Ifos.



Aldo Ifos.

Carboxy Ifos.

Ifos.Mustard



Acrolein

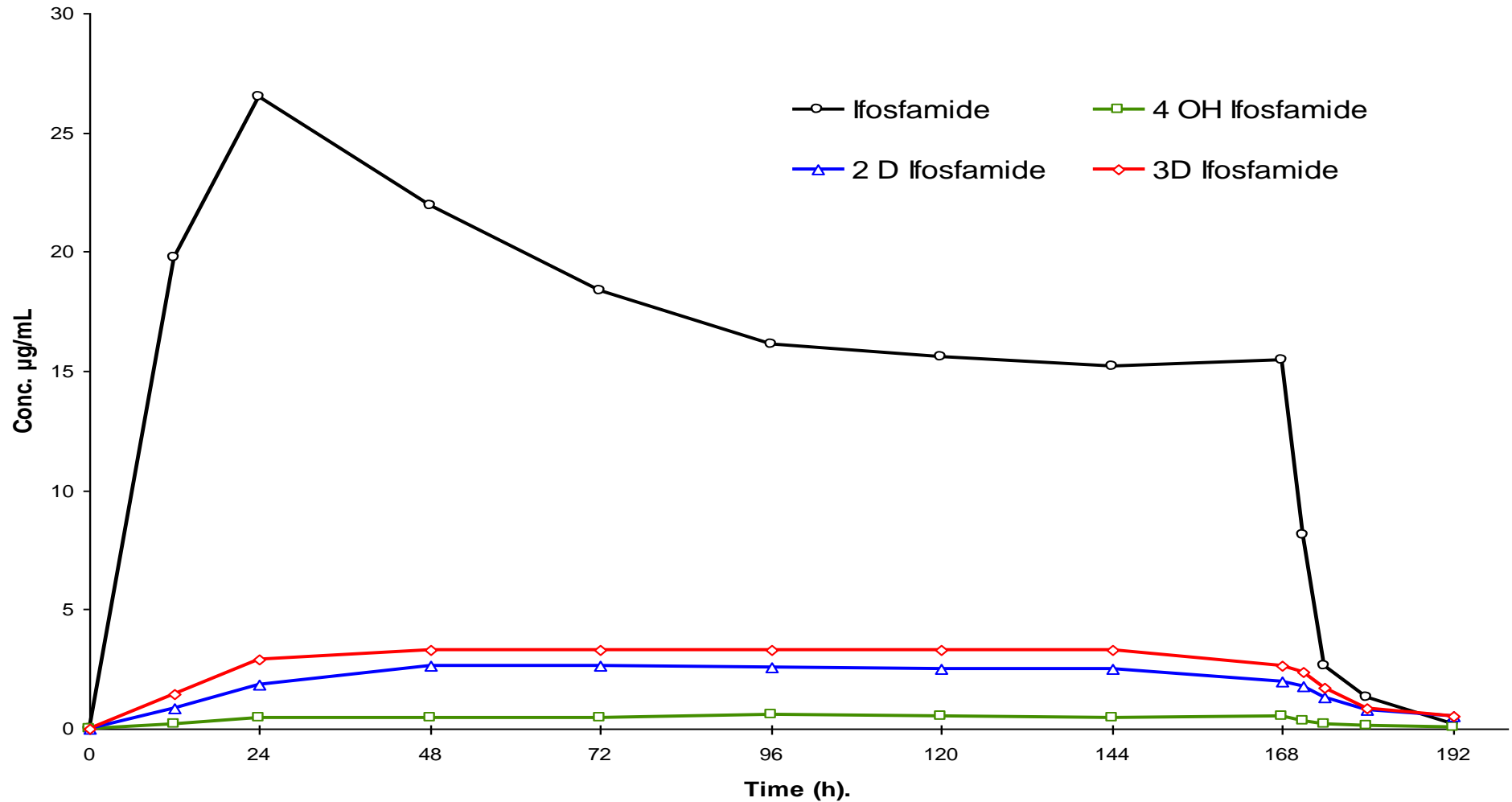
Alkylating Agents

ADN

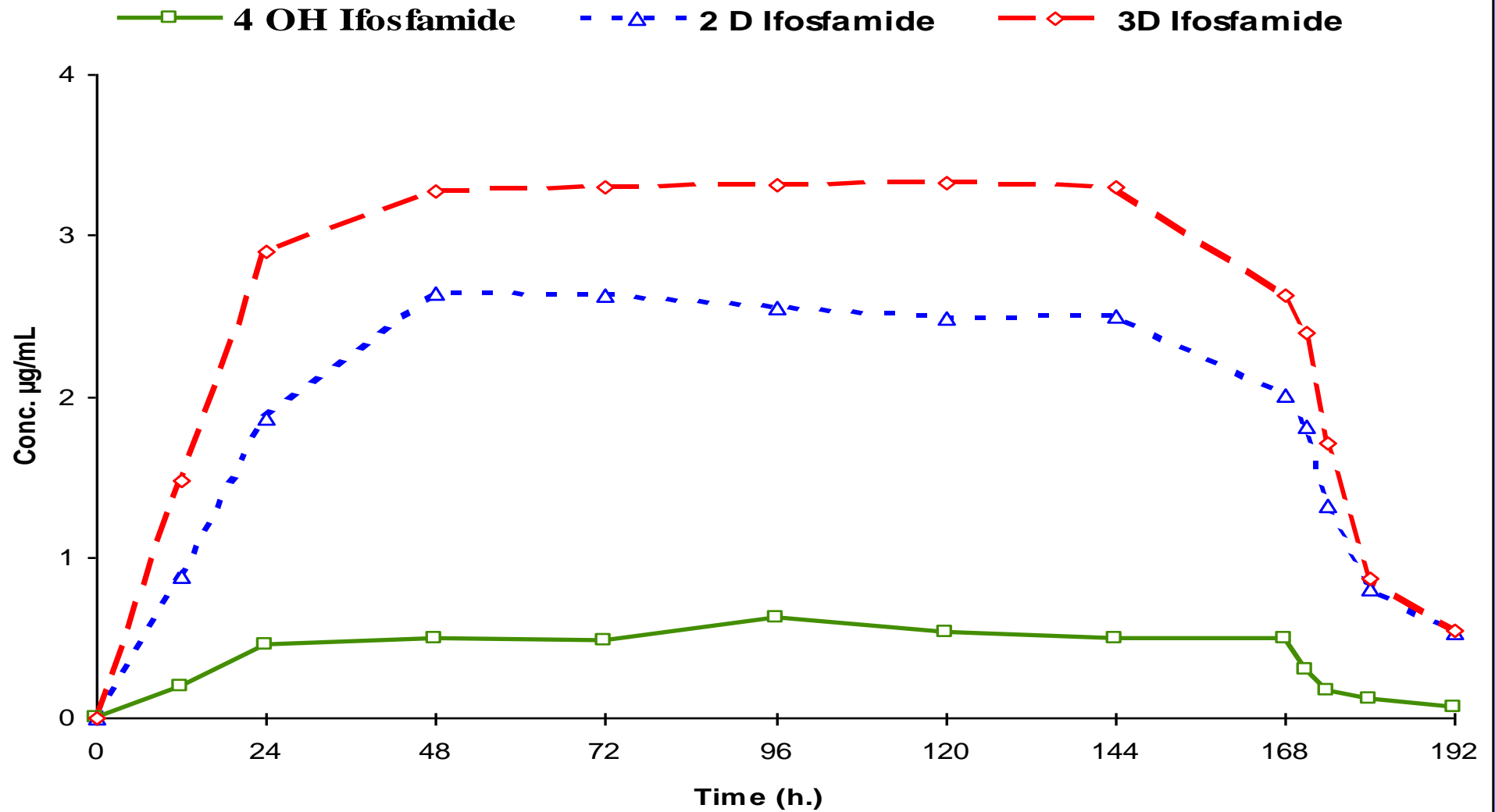
ADN



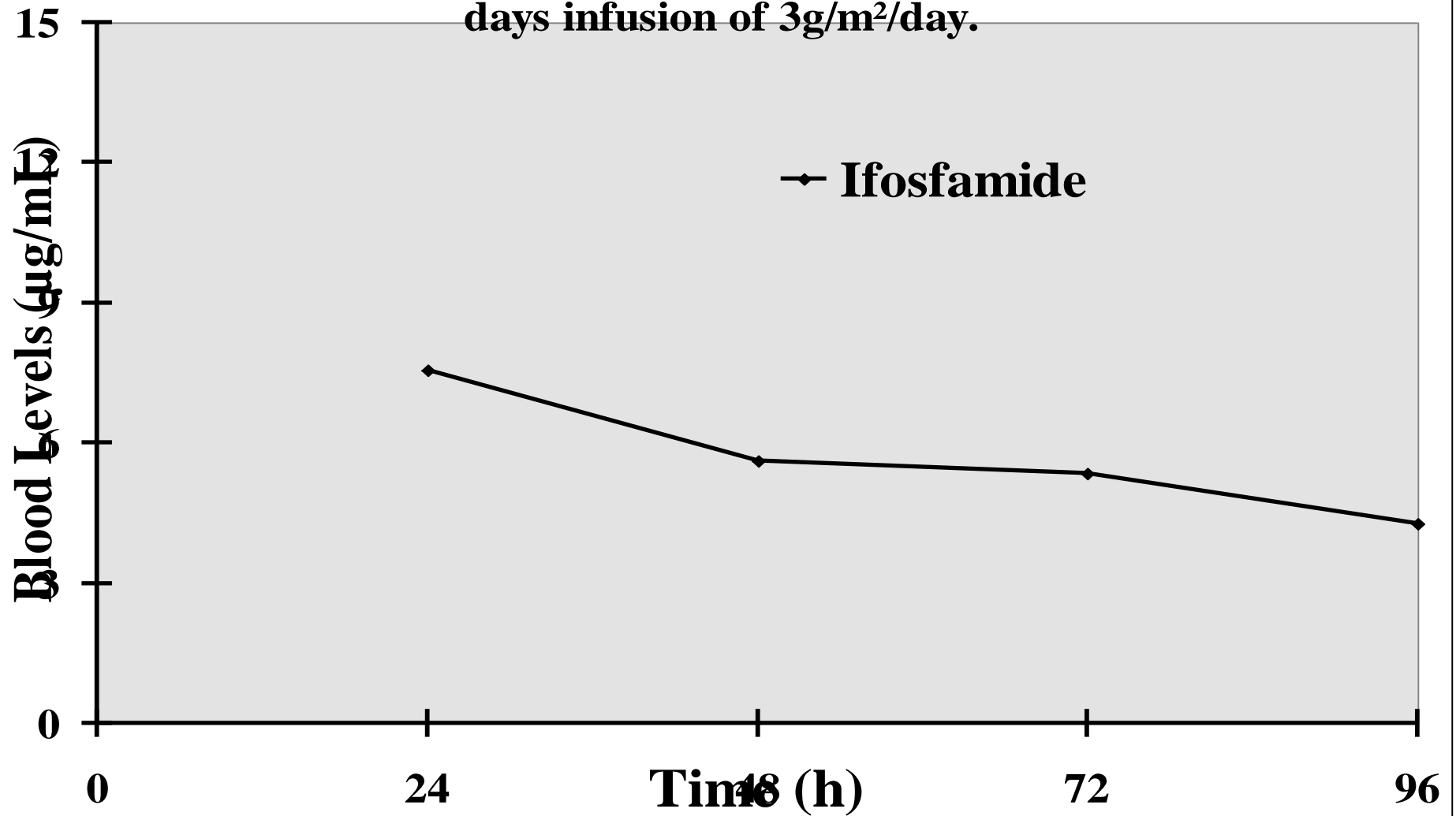
Continuous infusion in Children (3g/m²/d)



Continuous infusion in Children (3g/m²/d)



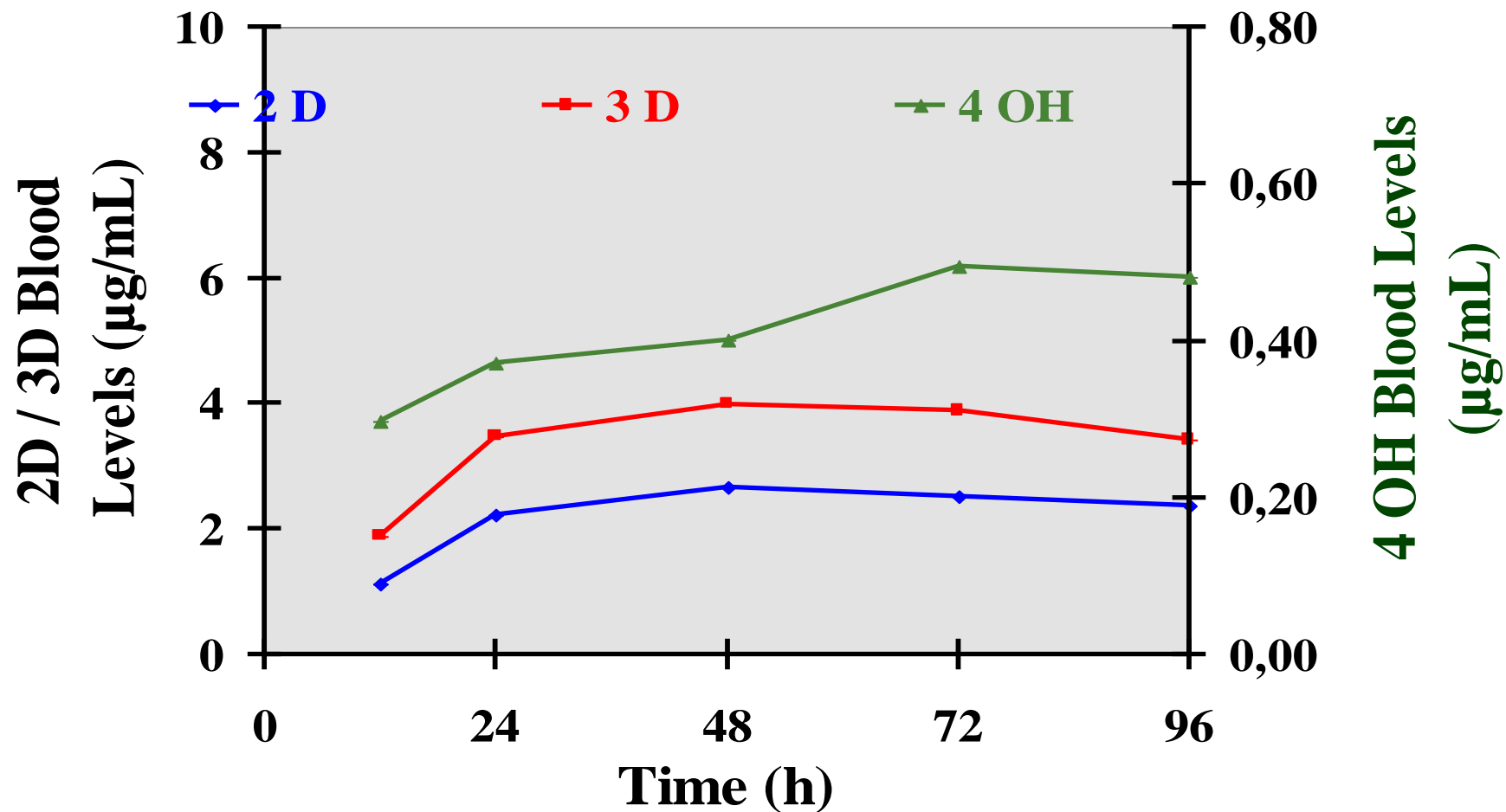
Mean Ifosfamide whole blood levels observed during a 4 days infusion of 3g/m²/day.



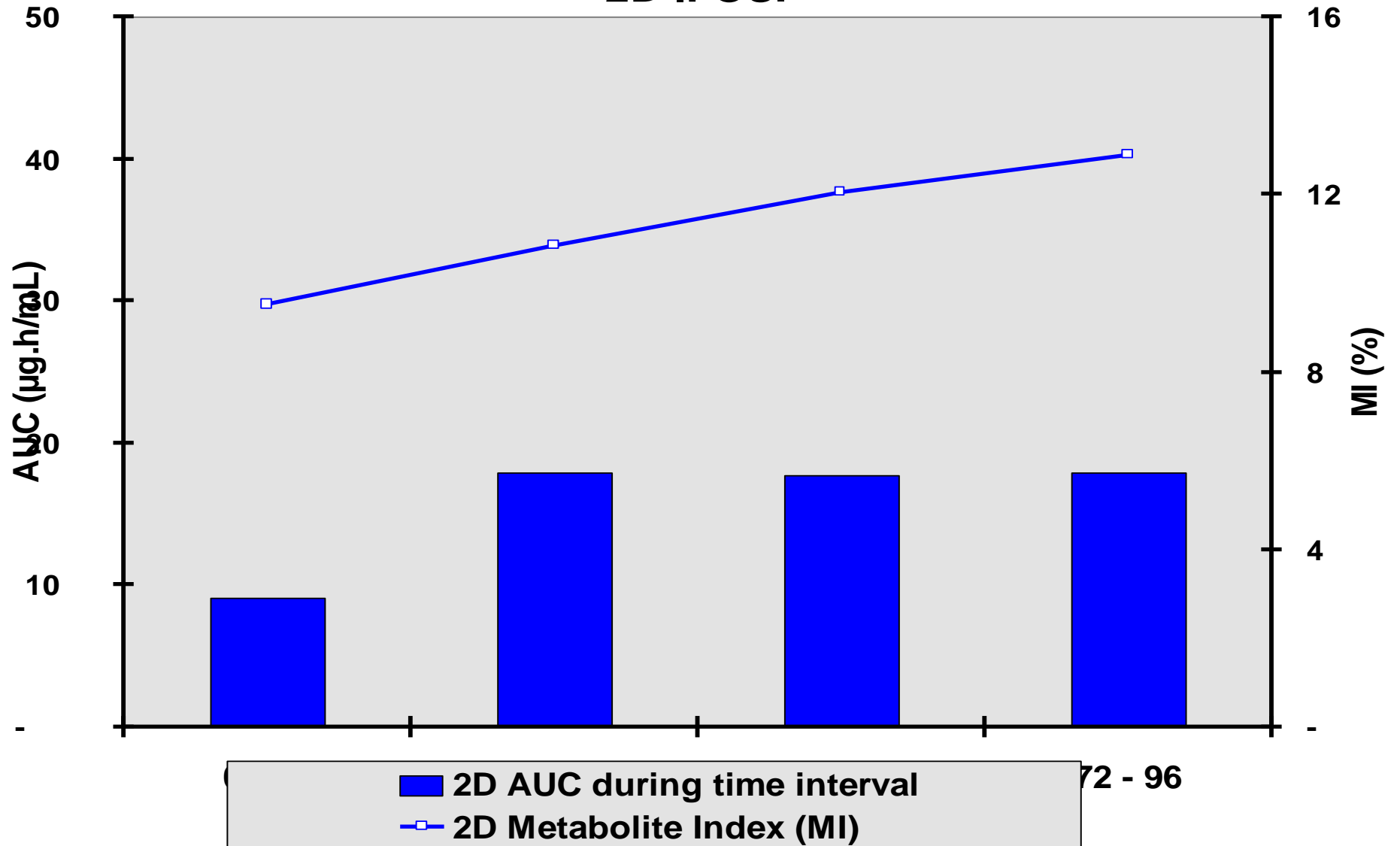
Concentration and A.U.C of Ifosfamide and Metabolites during the continuous infusion

| n=40 | Conc 24 h | Conc 48 h | Conc 72 h | Conc 96 h | A.U.C 0- 24h | A.U.C 24- 48h | A.U.C 48- 72h | A.U.C 72- 96h |
|-----------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Ifos/ Dose | 7.55 +/- 4.81 | 5.66 +/- 3.46 | 5.12 +/- 4.56 | 3.93 +/- 3.85 | 91.3 +/- 63.9 | 158.7 +/- 94.7 | 132.7 +/- 90.6 | 122.1 +/- 91.0 |
| 2d Ifos | 2.23 +/- 1.24 | 2.65 +/- 1.14 | 2.52 +/- 1.05 | 2.38 +/- 0.77 | 9.1 +/- 12.1 | 17.9 +/- 15.9 | 17.8 +/- 12.2 | 17.9 +/- 12.3 |
| 3d Ifos | 3.46 +/- 1.45 | 3.99 +/- 1.48 | 3.88 +/- 1.21 | 3.41 +/- 1.04 | 13.6 +/- 12.7 | 27.3 +/- 18.4 | 27.8 +/- 18.3 | 25.1 +/- 20.4 |
| 4OH Ifos | 0.37 +/- 0.19 | 0.40 +/- 0.16 | 0.50 +/- 0.21 | 0.48 +/- 0.24 | 1.6 +/-1.7 | 3.1 +/-2.4 | 3.4 +/-2.7 | 3.5 +/-2.8 |

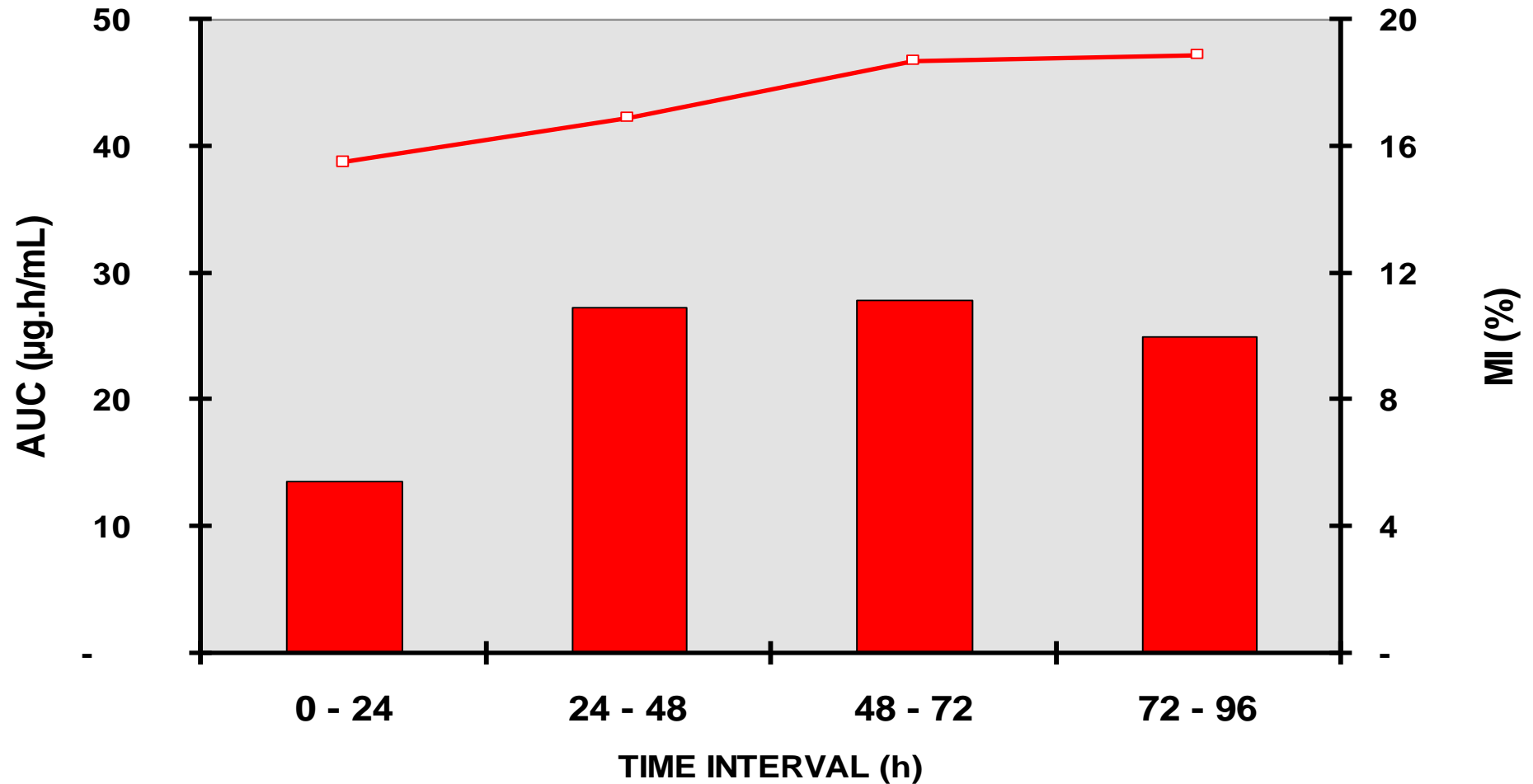
**Mean Ifosfamide Metabolites whole blood levels
during a 4 days infusion of 3g/m²/day.**



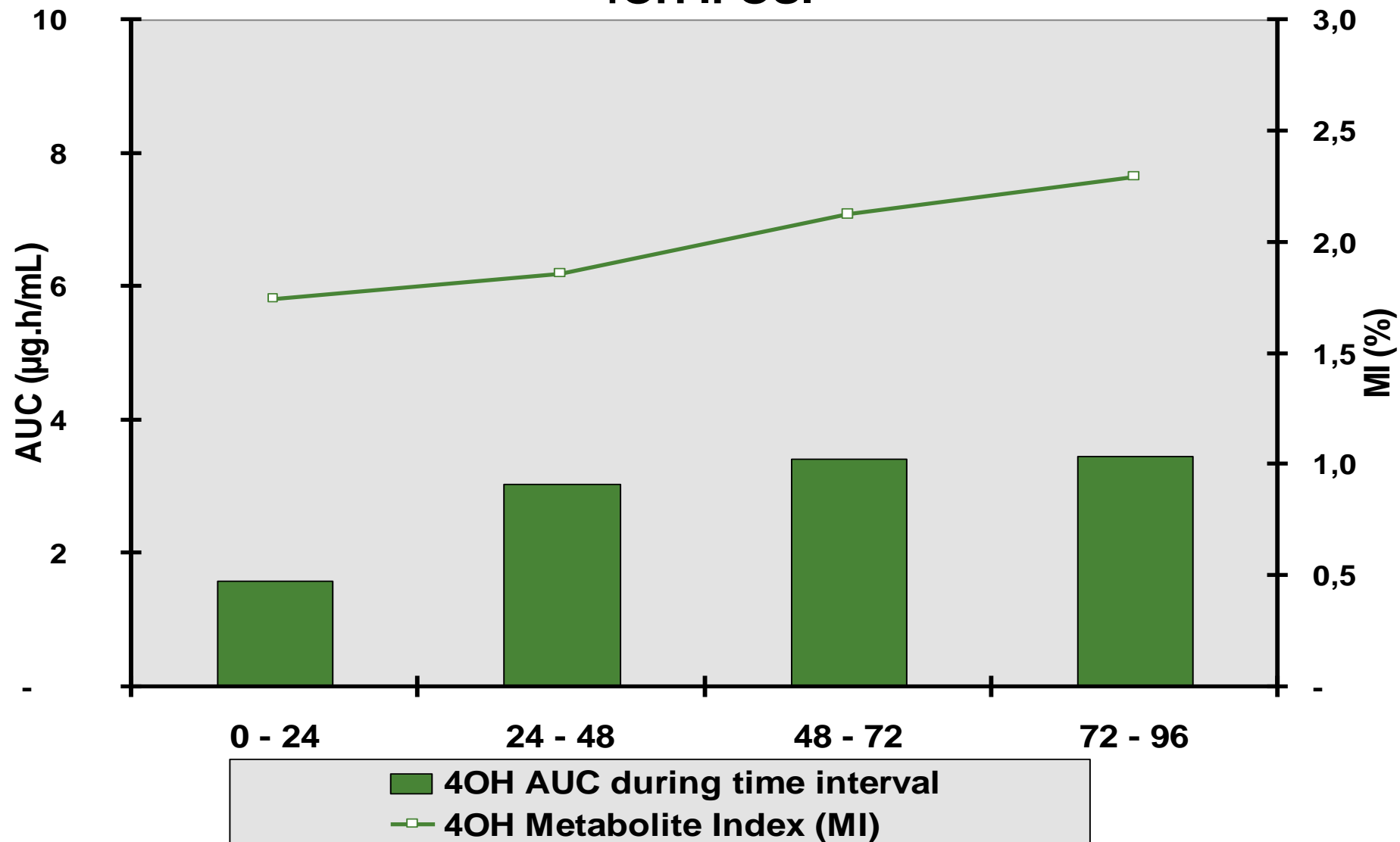
2D IFOS.



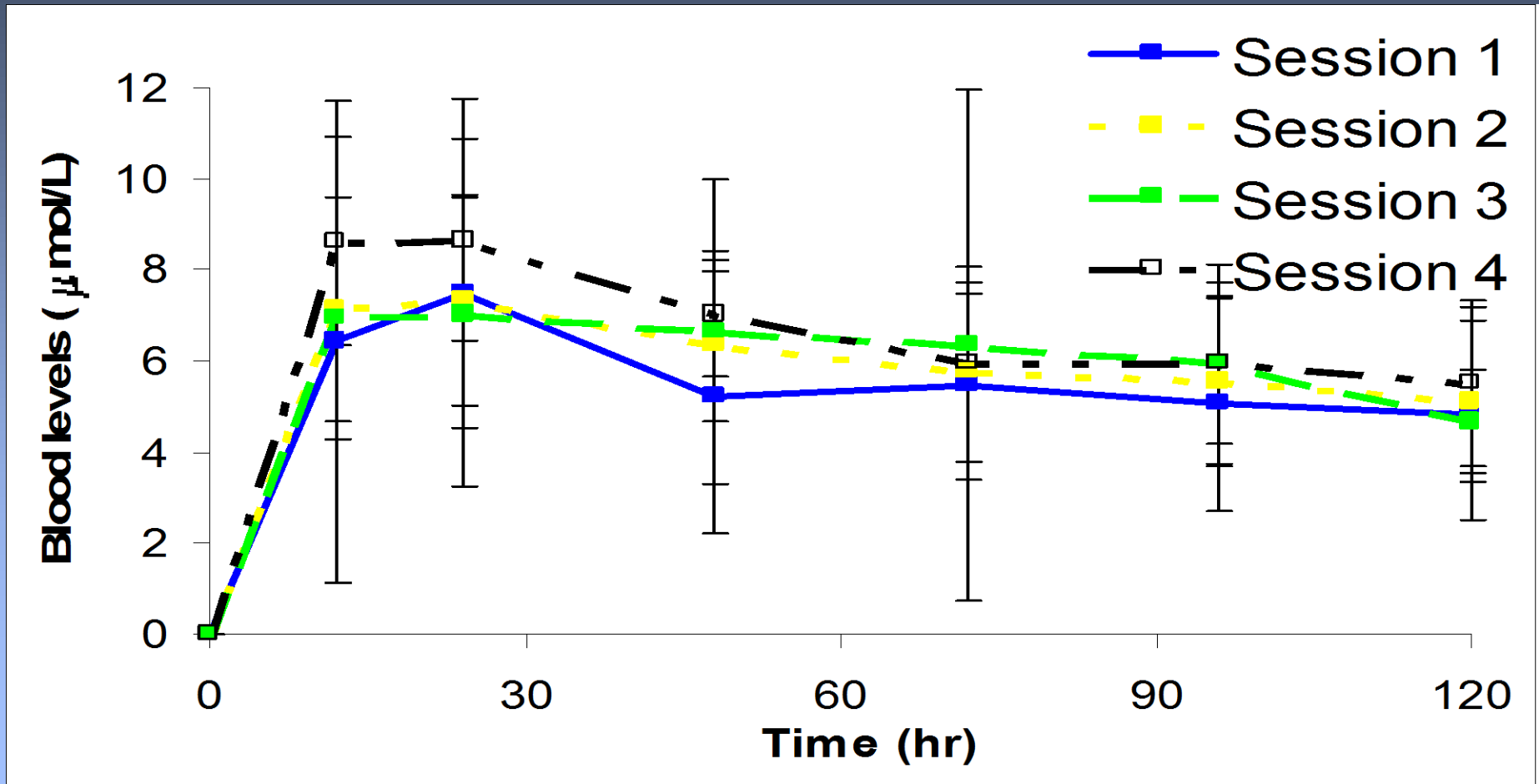
3D IFOS.



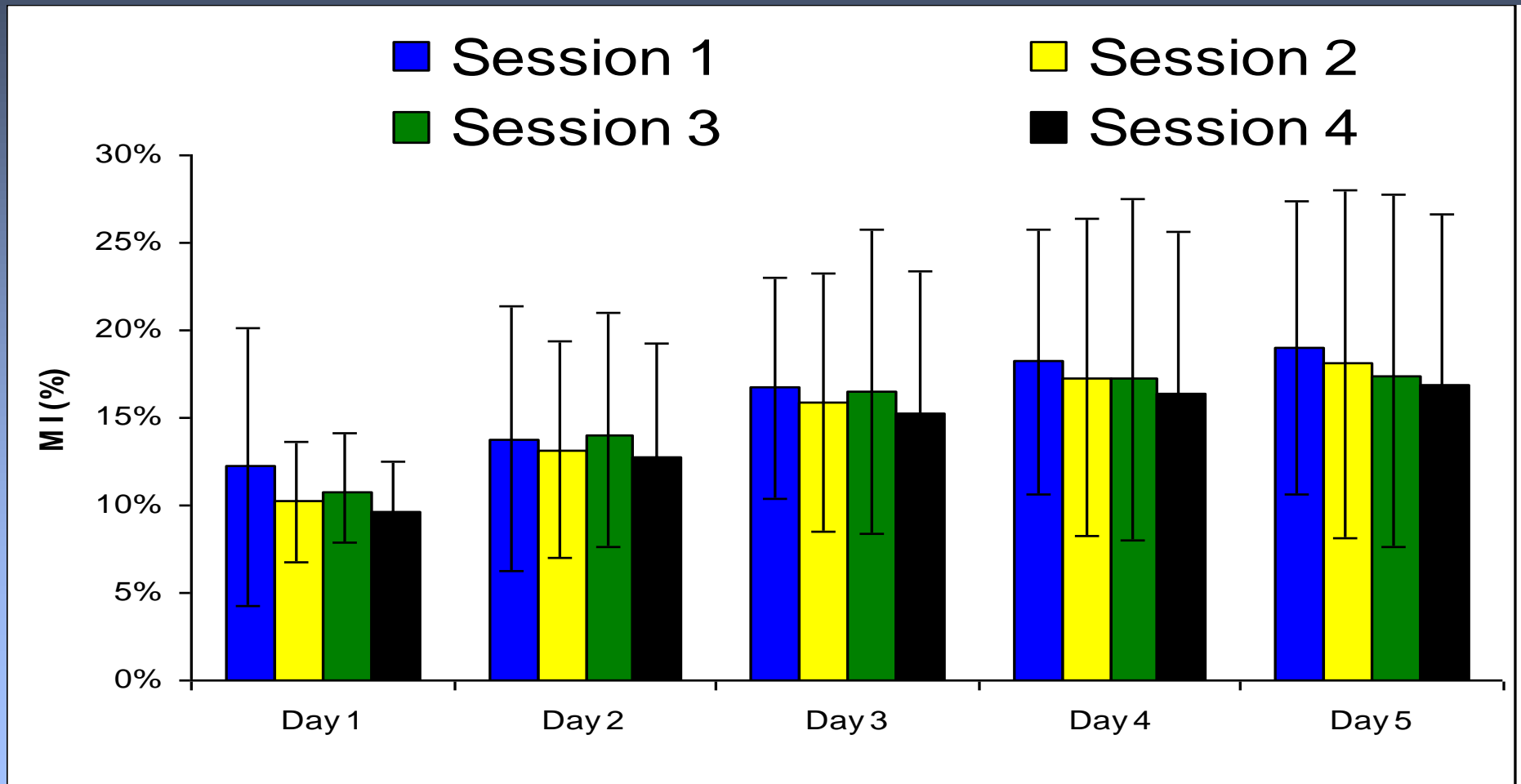
4OH IFOS.



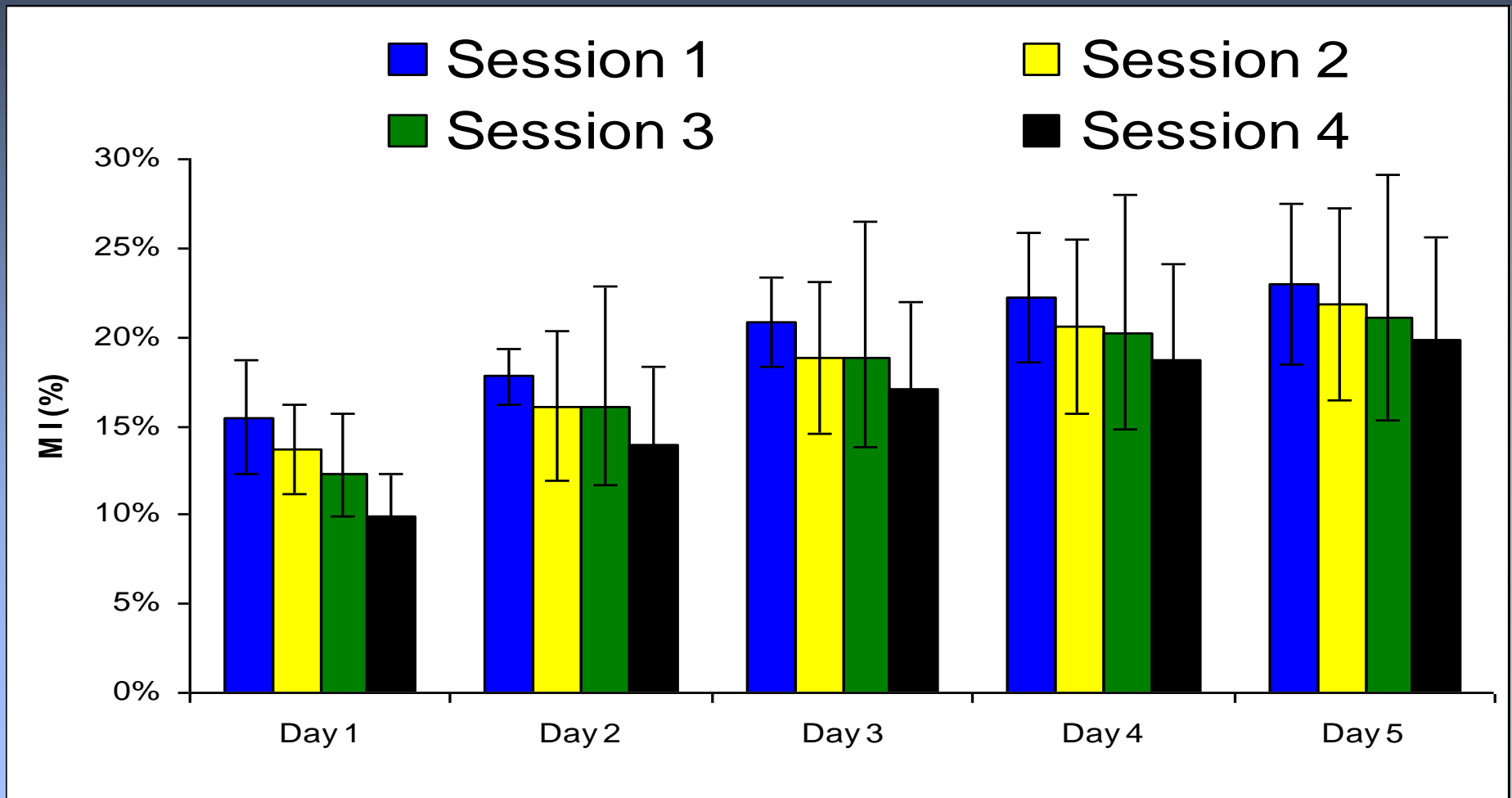
Pharmacokinetic profiles of ifosfamide during a 5 days continuous infusion of ifosfamide (Values are dose corrected) in 7 patients.



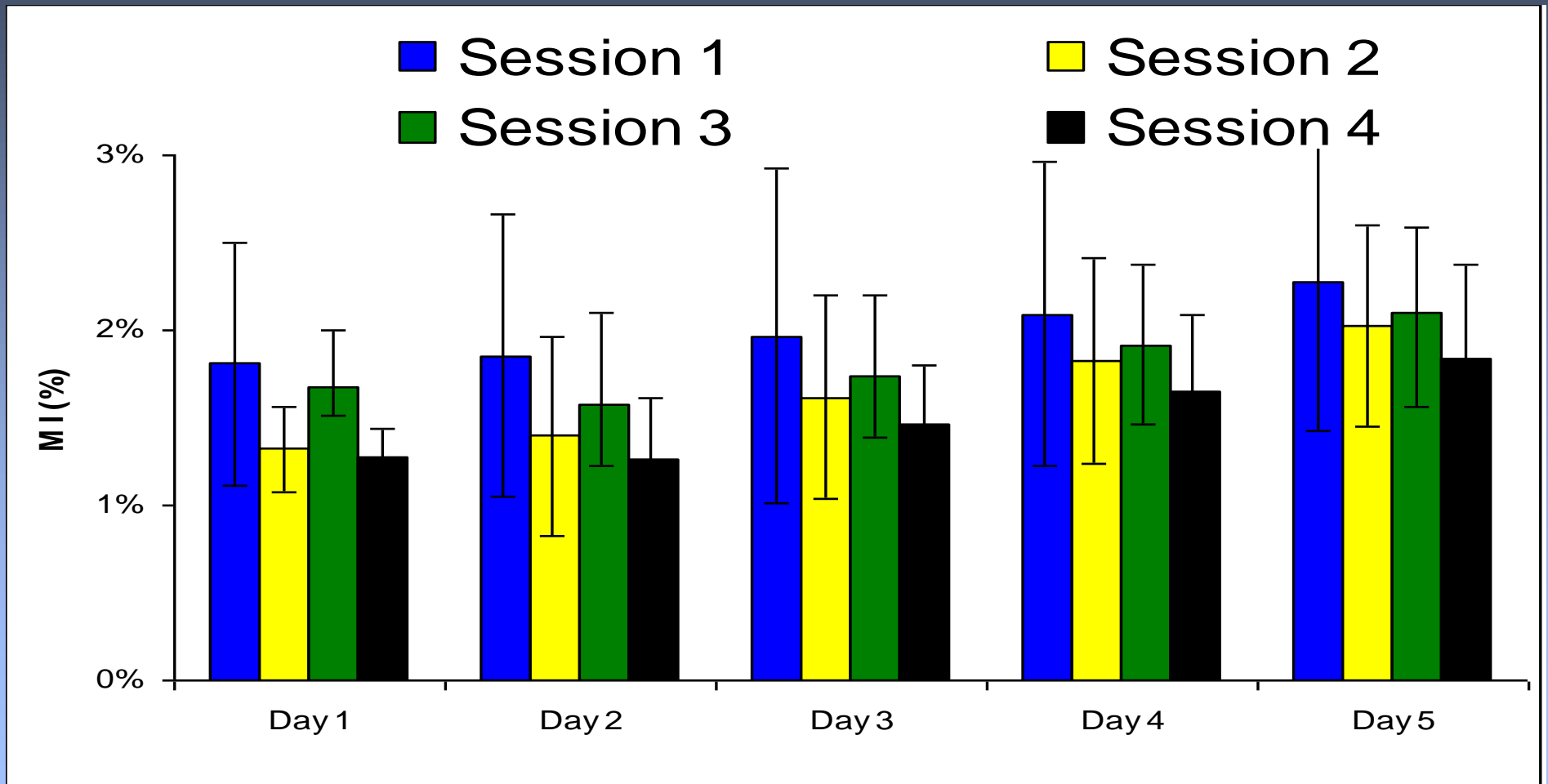
Variations of the Metabolite Index (MI %) of 2D Ifosfamide.



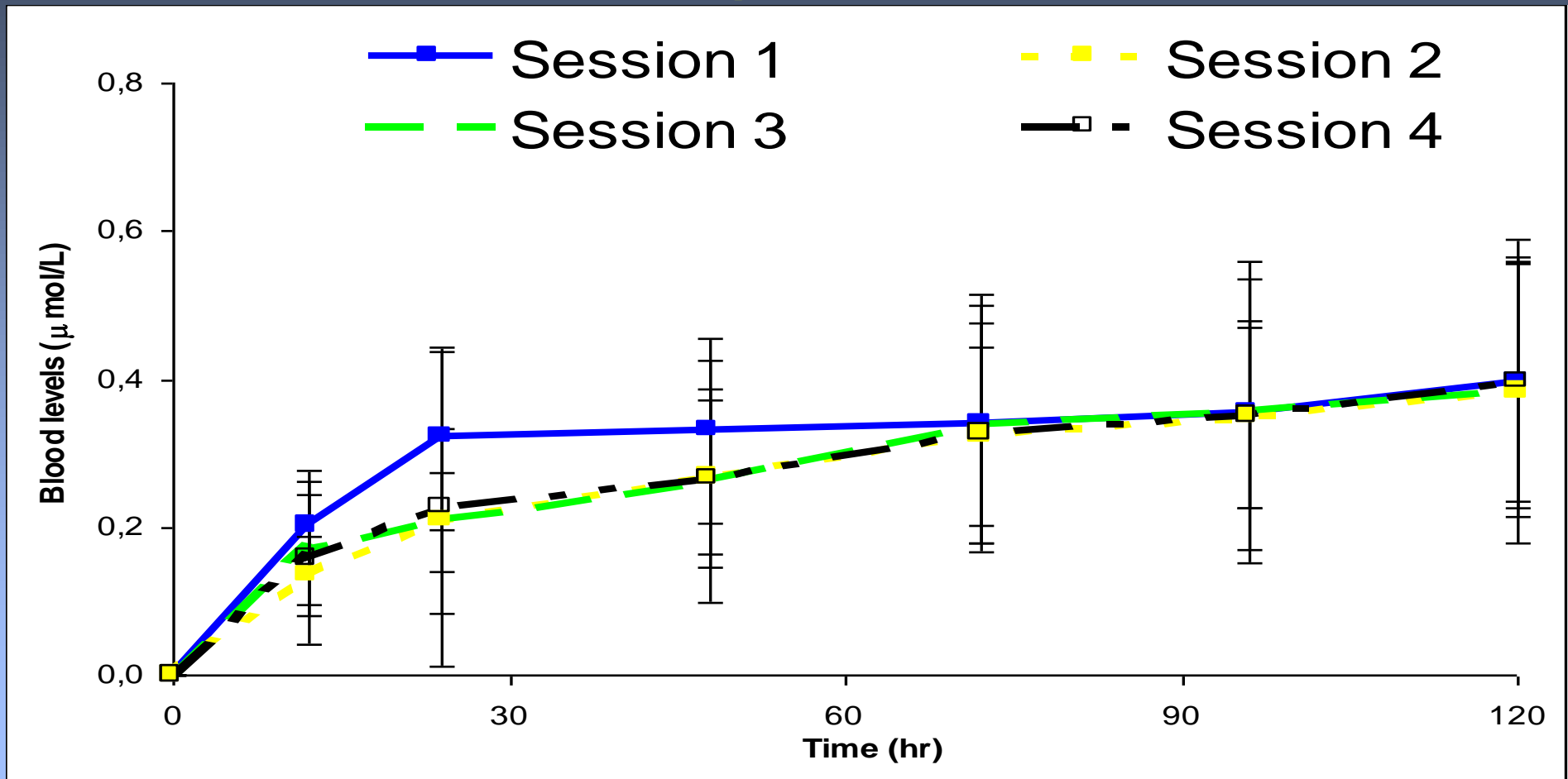
Variations of the Metabolite Index (MI %) of 3D Ifosfamide.

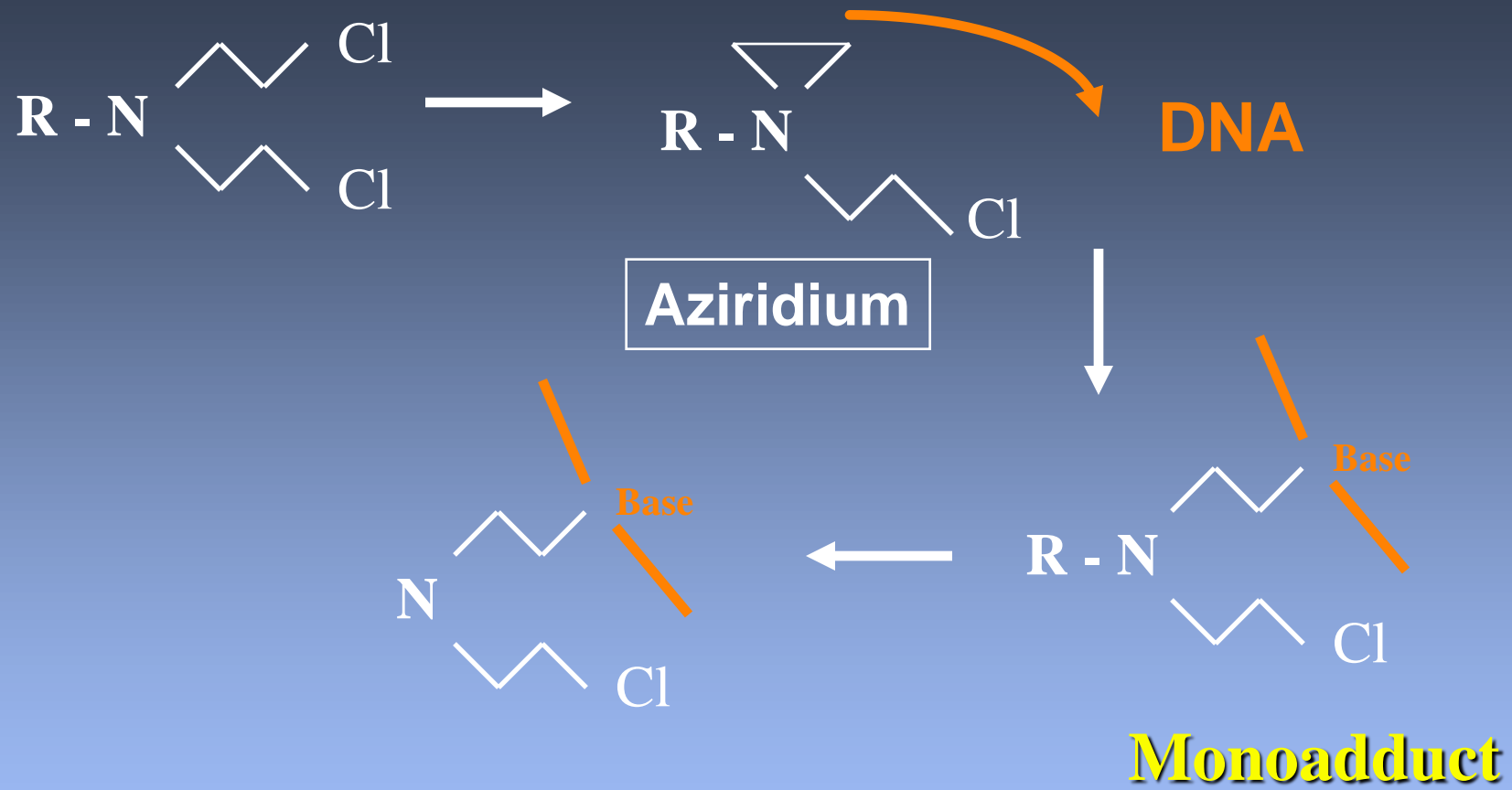


Variations of the Metabolite Index (MI %) of 4-Hydroxy Ifosfamide.

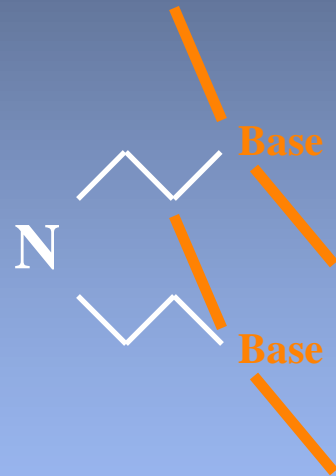
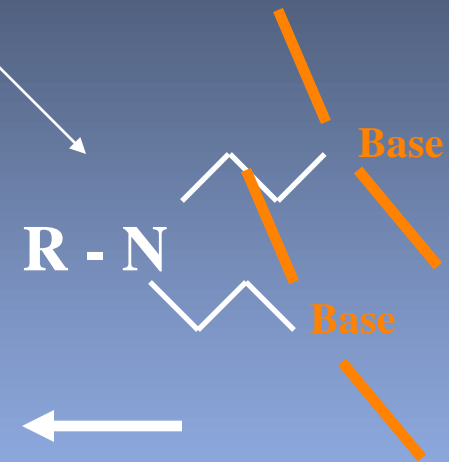
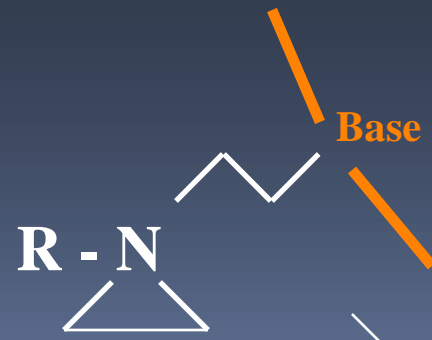
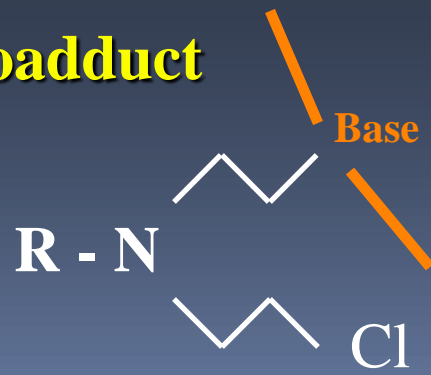


Pharmacokinetic profiles of 4 Hydroxy ifosfamide during a 5 days continuous infusion of ifosfamide in 7 patients.

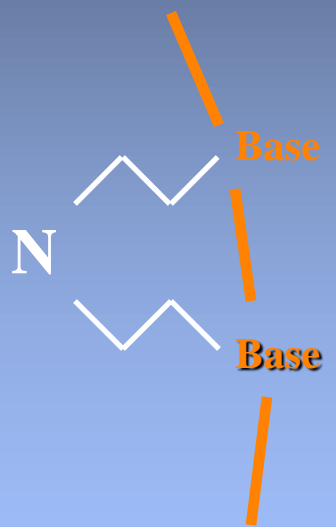




Monoadduct



Interstrand Crosslink



Intrastrand Crosslink