MICROALGAS

“Simposio de cianobacterias y cianotoxinas: Impacto ambiental, implicaciones en salud pública y potencial Biofarmacéutico.”

ITESO

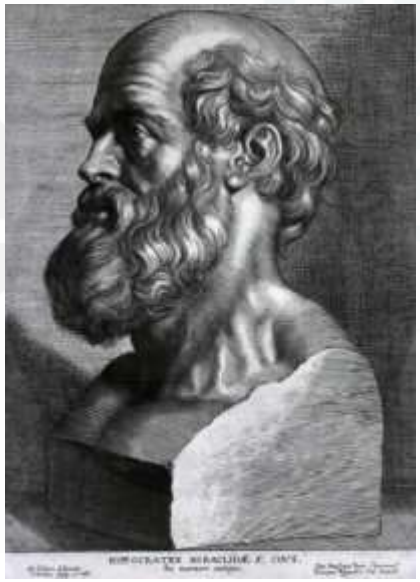
Introdução a toxicologia das cianotoxinas

Valéria Freitas de Magalhães

Ana de la Cueva

HISTÓRICO

- **Pré-história** – plantas venenosas e seguras
- **Venenos** – caça, guerras e assassinatos
- **"Ebers Papyrus" (1.500 a.C.)** – registro de cerca de 800 princípios ativos. Informações sobre venenos conhecidos como: cicuta, opium e metais (Pb, Cu etc)



- **Hipócrates (400 a.C.)** - introduziu princípios toxicologia clínica, descrevendo conceitos elementares da biodisponibilidade e overdose.

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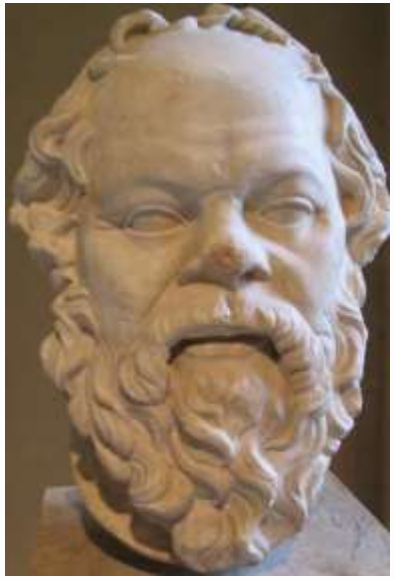

O uso de venenos como um método de execução foi claramente exemplificada por **Sócrates (470-399 aC),** cuja morte por envenenamento por cicuta parece ter sido o resultado de um cálculo de dose-resposta correta.

- O uso de intoxicações continuava parte importante da vida durante a Idade Média. Durante este período, o uso de venenos era uma maneira comum de eliminar candidatos políticos, cônjuges e competidores. Ex: Toffana (séc XVII), os Bórgias (séc XV e XVI) e os Medicis (XV e XVII) .

- **Paracelsus (1493-1541)**

Suas teorias levam à postulação de vários conceitos que lembram o que hoje é chamado de toxicologia

Descreve o princípio de que a dose faz o veneno. Toxidade relacionada a dose.

"Todas as substâncias são venenosas, a dose correta diferencia o veneno do remédio"

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➢ Grandes marcos

✓ **Rev Industrial** (XVIII e XIX)

✓ **Séc XX**

- Grandes Guerras
- síntese de novos compostos "*mágicos*":
  DDT (Primavera silenciosa – Rachel Carson 1962).

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- danos e acidentes – talidomida (1960's)
- 1960's avaliação de risco
- sofisticação dos métodos de detecção
- Love canal (1970's) usado como aterro de 21.000 ton de rejeitos tóxicos pela Hooker Chemical (atual Occidental Petroleum Corporation).

- Pacific Gas & Oil (PG&O) – Cr VI em água subterânea

Erin Brockovich

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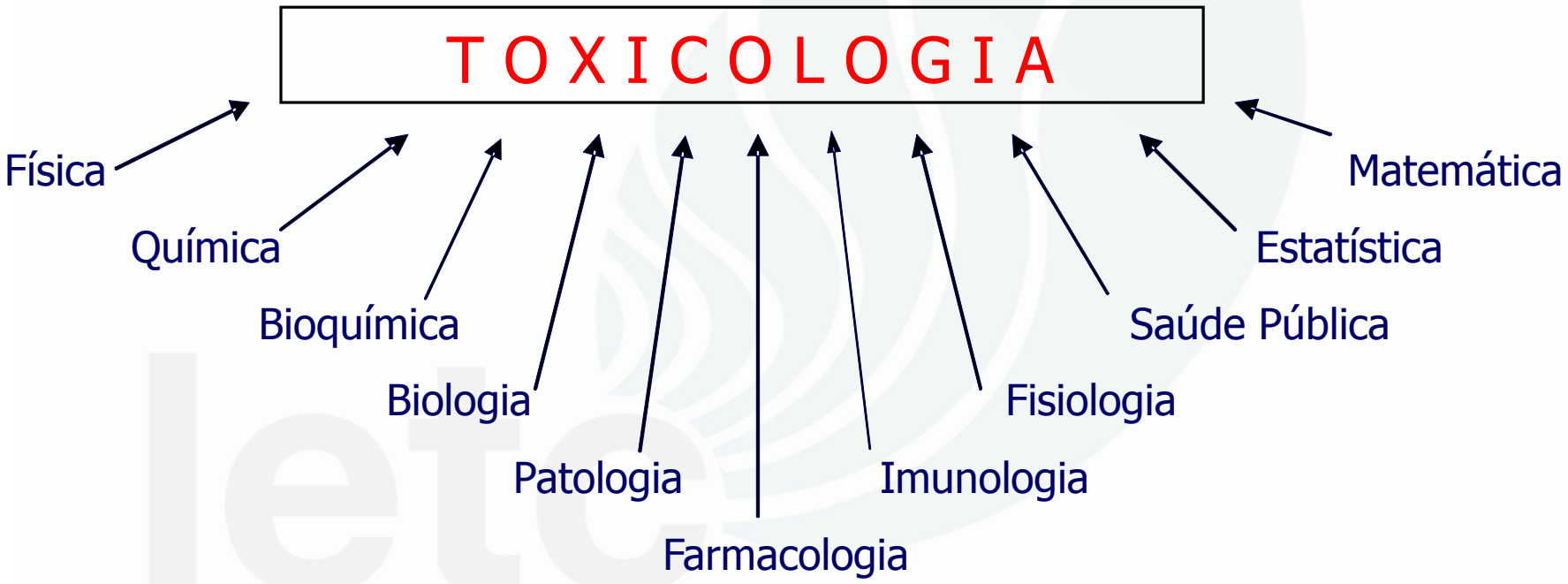
Estudo de efeitos adversos de químicos em organismos vivos



INTERDISCIPLINAR

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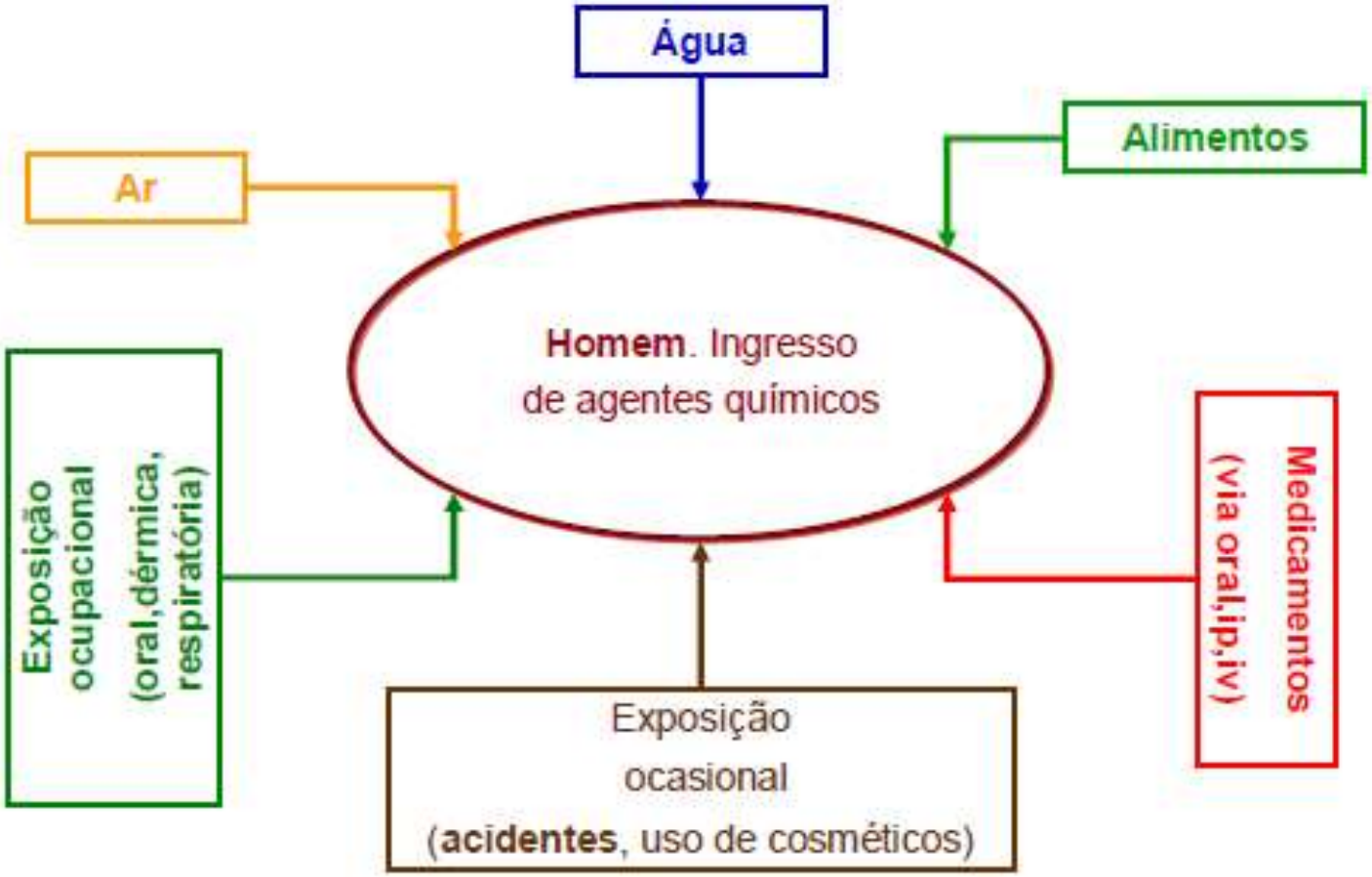
Água
Alimentos
Ar
Homem. Ingresso de agentes químicos
Exposição ocupacional (oral,dérmica, respiratória)
Medicamentos (via oral,ip,iv)
Exposição ocasional (acidentes, uso de cosméticos)

Deve-se considerar:

✓ Propriedades físico-químicas da substância, impurezas e contaminantes

✓ Magnitude
✓ Duração
✓ Frequência
} da exposição

✓Vias de introdução

✓Organismo: espécie, linhagem, fatores genéticos, fatores imunológicos, estado nutricional, dieta; sexo, estado hormonal, idade, peso corpóreo; estado emocional, estado patológico (toxicocinética e toxicodinâmica)

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EXPOSIÇÃO – TOXICOCINÉTICA – TOXICODINÂMICA - CLÍNICA

EXPOSIÇÃO	TOXICOCINÉTICA	TOXICODINÂMICA	CLÍNICA
via/rota	absorção	interação	sintomas
freqüência	distribuição		alterações
duração	armazenemento		
dose	biotransformação (destoxificação/bioativação)		
concentração	eliminação		
prop físico-química			
suscetibilidade individual			
Disponibilidade			

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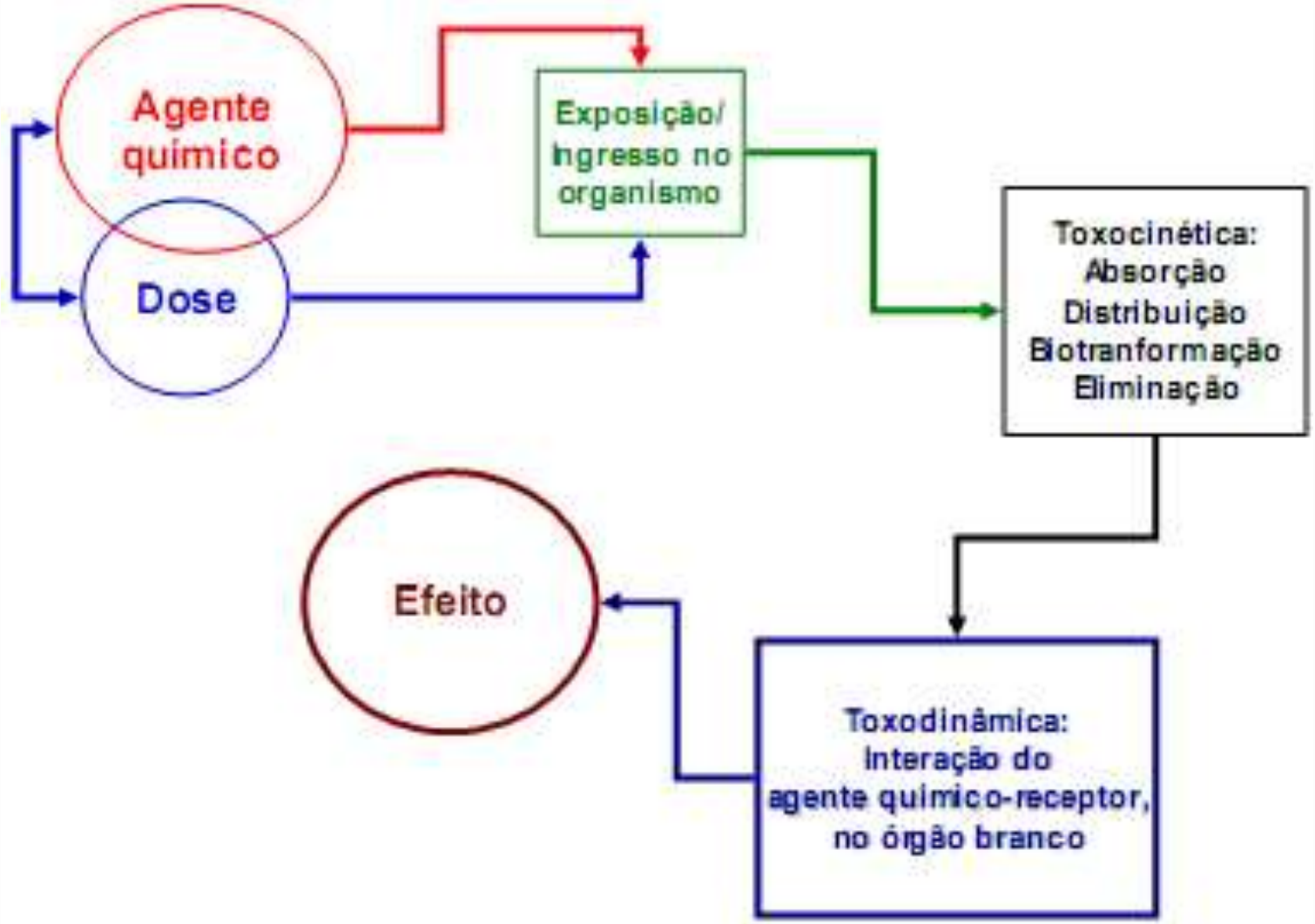
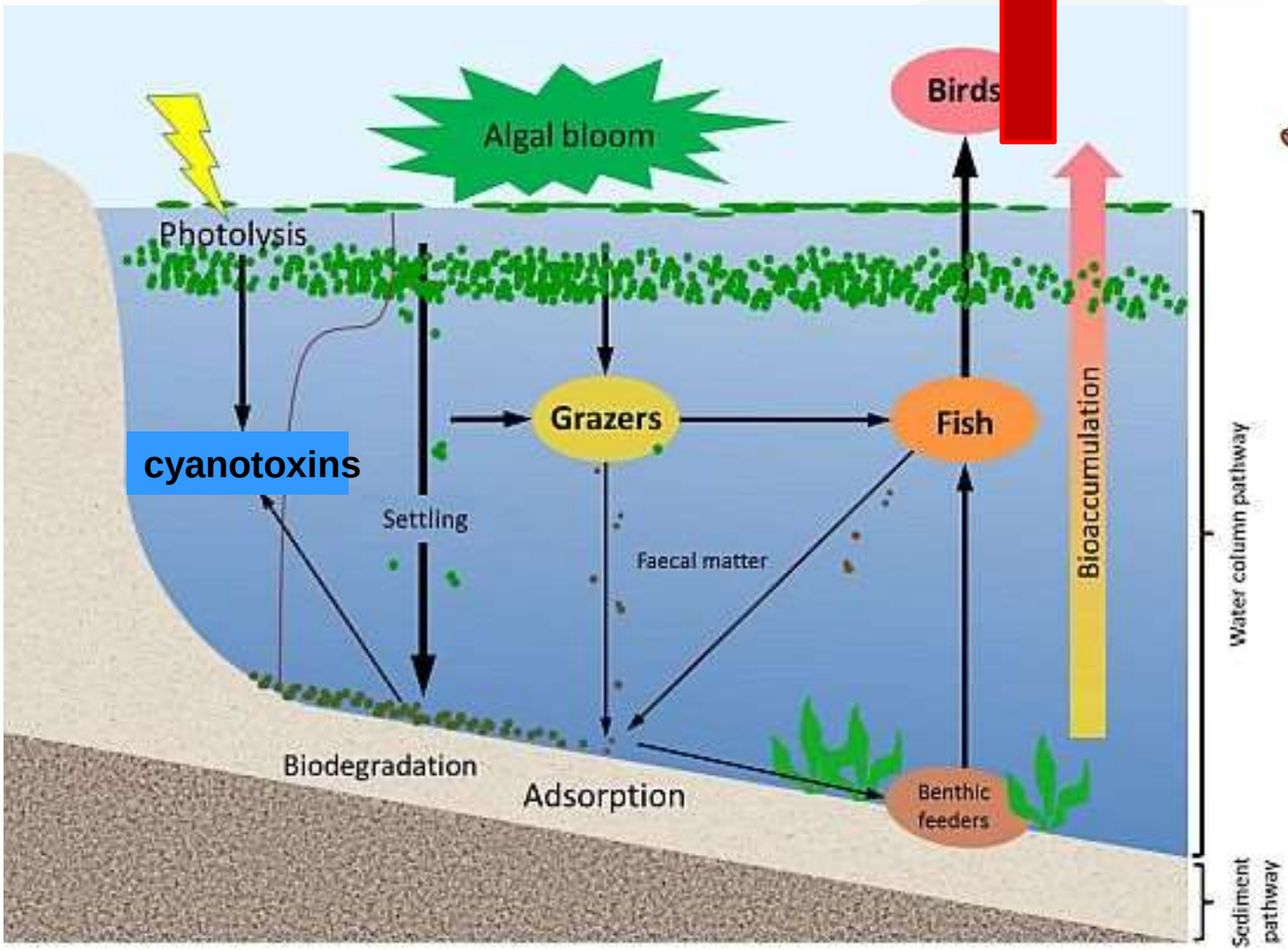
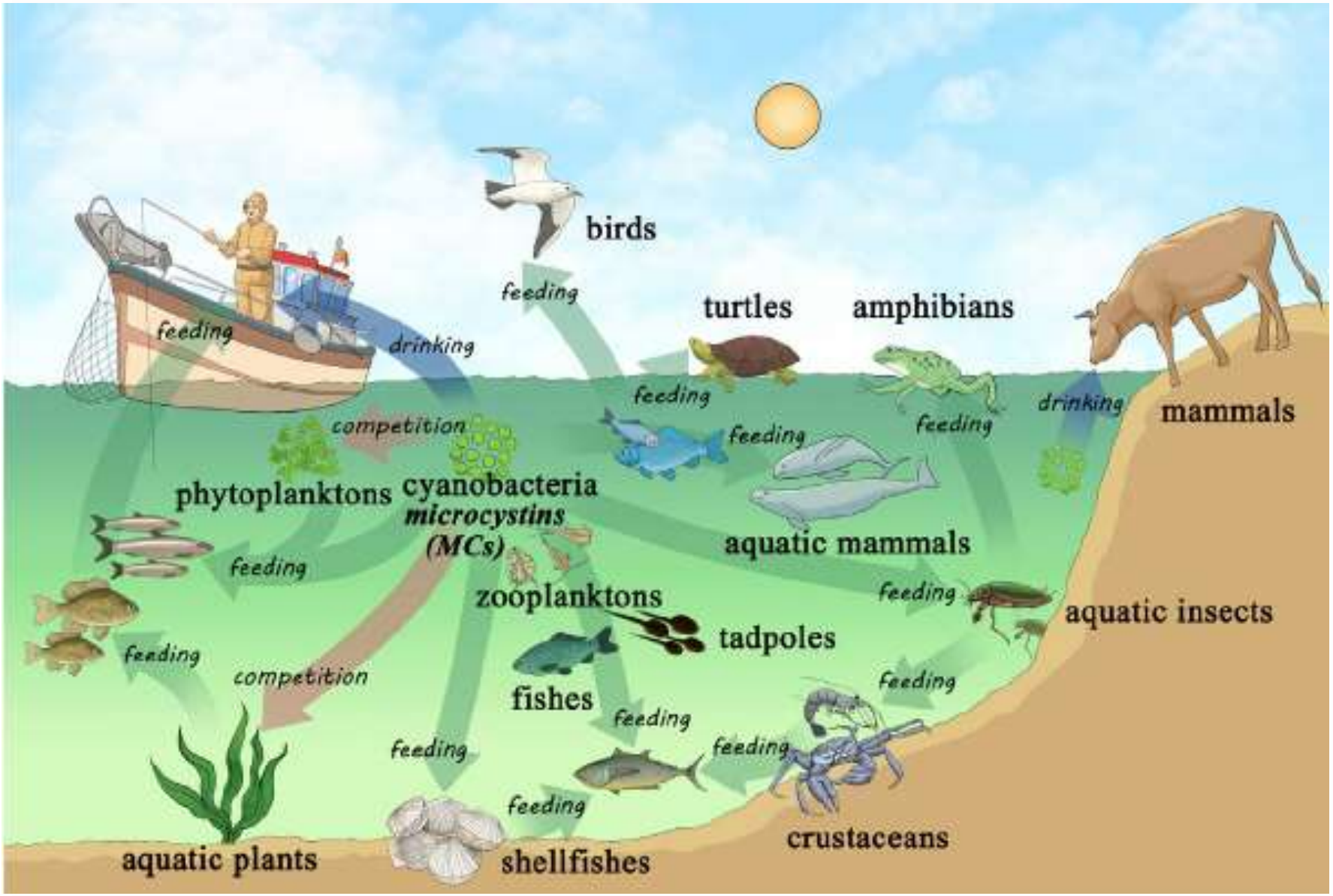

Agente químico
Dose
Exposição/ Ingresso no organismo
Toxocinética: Absorção Distribuição Biotranformação Eliminação
Efeito
Toxodinâmica: Interação do agente químico-receptor, no órgão branco

cianotoxinas



https://pt.depositphotos.com/46241971/stock-illustration-cartoon-caveman.html

Song et al (2015)



Chen et al 2016

Exposição humana

Vias de introdução:

Oral

- água
- Alimento (bioacumulação)
- Atividades Recreacionais

Inalação

- Atividades Recreacionais
- Atividades Profissionais

Intravenosa

- Diálise Renal
- Parenteral

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Exposição oral, dérmica, recreacional e inalação

O Globo 11/11/04

Através de alimentos

O Globo 13/08/2001

https://www.mrsaltwatertank.com/quarantine

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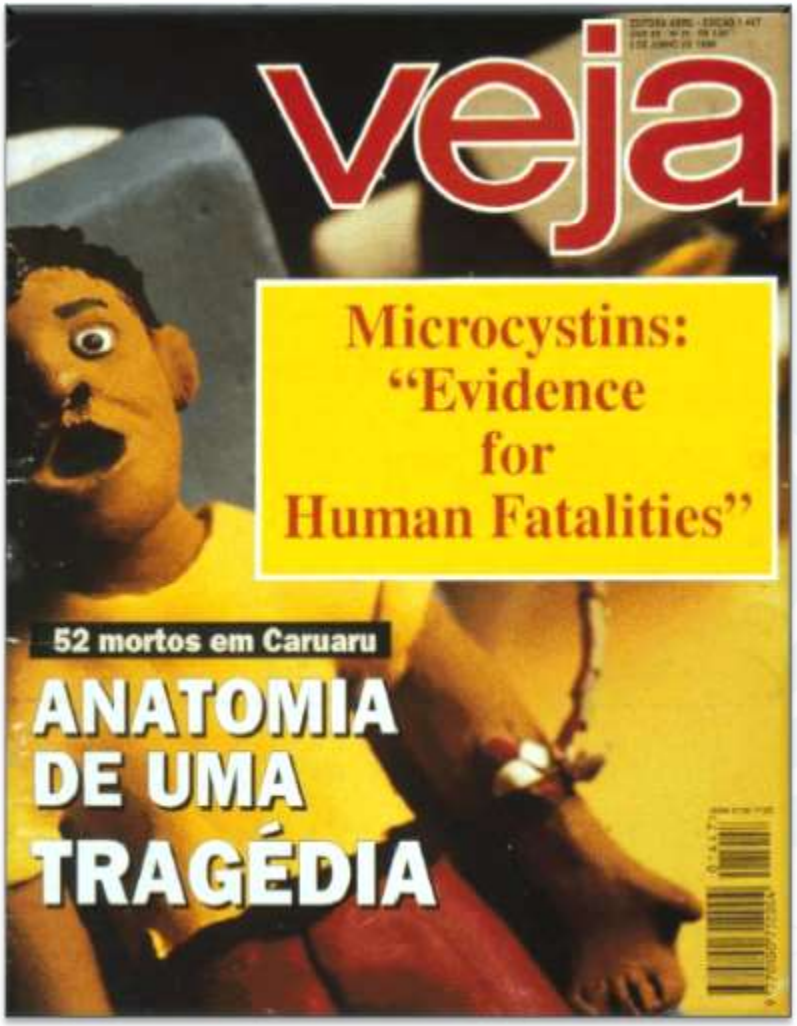

Através da hemodiálise

TOXINAS DE CIANOBACTÉRIAS

NEUROTOXINAS

- Anatoxina-a
- Anatoxina-a(s)
- Saxitoxinas

HEPATOTOXINAS

- Nodularina
- Microcistinas

CITOTOTOXINAS

- Cilindrospermopsina

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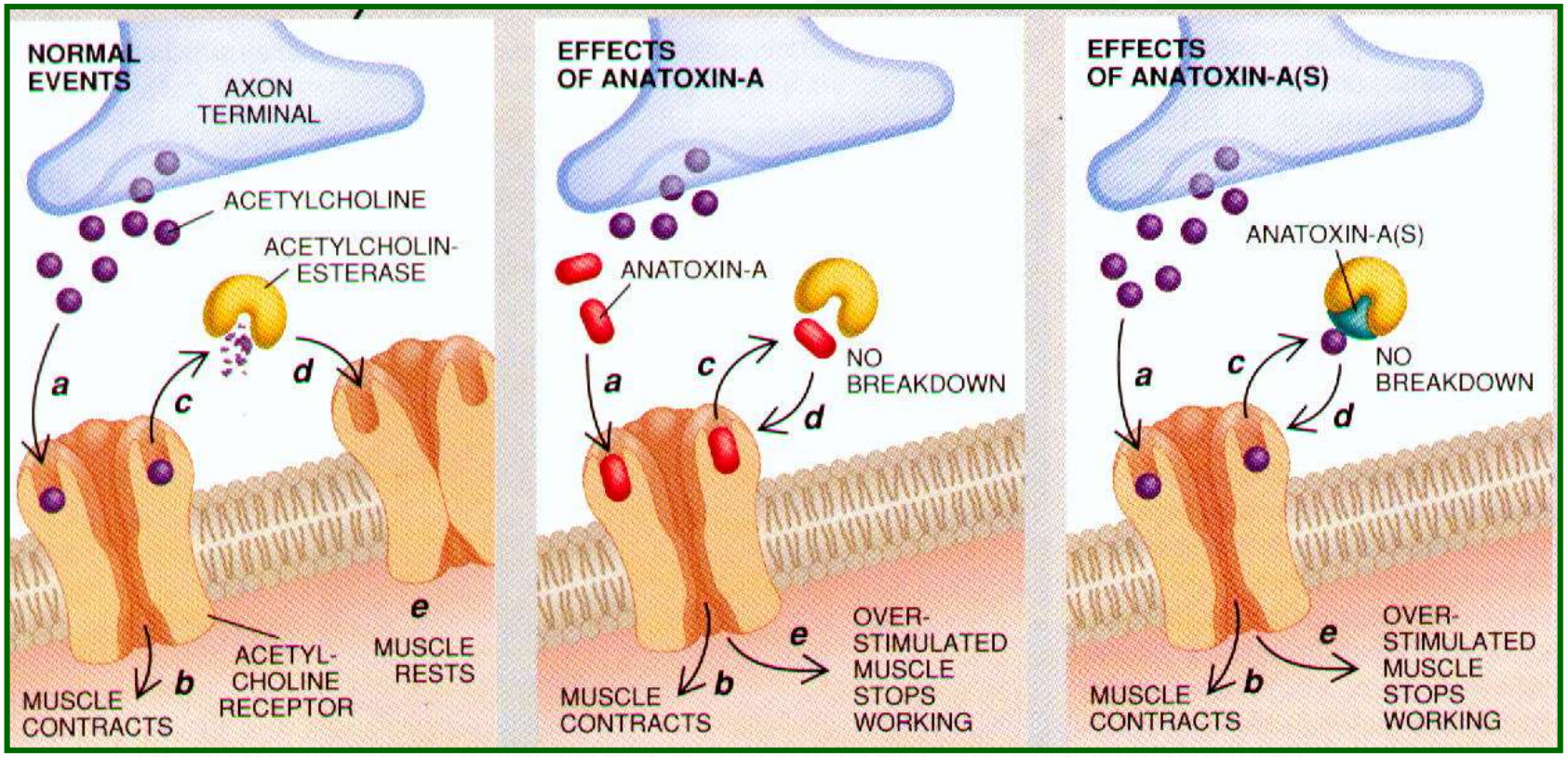
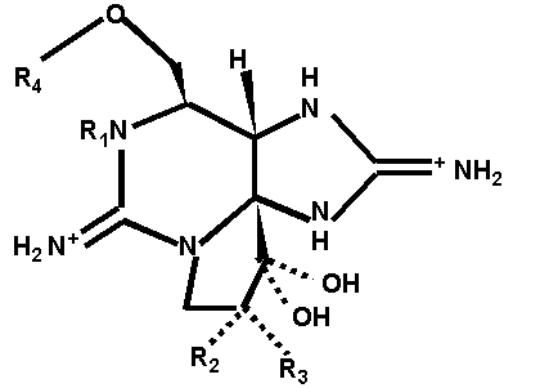
MECANISMO DE AÇÃO: ANATOXINA a e a(s)



Carmichael, 1994



ESTRUTURA DAS SAXITOXINAS

R1	R2	R3	Carbamatos R4: CONH2	N-Sulfocarbamoil R4: CONHSO3-	Decarbamoil R4: H
H	H	H	STX	GTX5	dcSTX
OH	H	H	NeoSTX	GTX6	dcneoSTX
OH	H	OSO_3^-	GTX1	C3	dcGTX1
H	H	OSO_3^-	GTX2	C1	dcGTX2
H	OSO_3^-	H	GTX3	C2	dcGTX3
OH	OSO_3^-	H	GTX4	C4	dcGTX4

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Table 1. *Cont.*

Toxin	R1	R2	R3	^n^R4	R5	Origin	Ref.
Deoxy-Decarbomoylated							
doSTX	H	H	H	H	OH	*G. catenatum*	[9,84]
doGTX1	OH	H	OSO_3^-	H	OH	*G. catenatum*	[9,84]
doGTX2	H	H	OSO_3^-	H	OH	*G. catenatum*	[9,84]
***L. wollei* toxins**							
LWTX1	H	H	OSO_3^-	$OCOCH_3$	H	*L. wollei*	[82]
LWTX2	H	H	OSO_3^-	$OCOCH_3$	OH	*L. wollei*	[82]
LWTX3	H	OSO_3^-	H	$OCOCH_3$	OH	*L. wollei*	[82]
LWTX4	H	H	H	H	H	*L. wollei*	[82]
LWTX5	H	H	H	$OCOCH_3$	OH	*L. wollei*	[82]
LWTX6	H	H	H	$OCOCH_3$	H	*L. wollei*	[82]
Mono-Hydroxy-Benzoate Analogs							
GC1	H	H	OSO_3^-	OCOPhOH	OH	*G. catenatum*	[83]
GC2	H	OSO_3^-	H	OCOPhOH	OH	*G. catenatum*	[83]
GC3	H	H	H	OCOPhOH	OH	*G. catenatum*	[83]
*GC4	OH	H	OSO_3^-	OCOPhOH	OH	*G. catenatum*	[85]
*GC5	OH	OSO_3^-	H	OCOPhOH	OH	*G. catenatum*	[85]
*GC6	OH	H	H	OCOPhOH	OH	*G. catenatum*	[85]
Di-Hydroxy Benzoate Analogs							
‡GC1a	H	H	OSO_3^-	DHB	OH	*G. catenatum*	[85]
‡GC2a	H	OSO_3^-	H	DHB	OH	*G. catenatum*	[85]
‡GC3a	H	H	H	DHB	OH	*G. catenatum*	[85]
‡GC4a	OH	H	OSO_3^-	DHB	OH	*G. catenatum*	[85]
‡GC5a	OH	OSO_3^-	H	DHB	OH	*G. catenatum*	[85]
‡GC6a	OH	H	H	DHB	OH	*G. catenatum*	[85]
Sulfated Benzoate Analogs							
‡GC1b	H	H	OSO_3^-	SB	OH	*G. catenatum*	[85]
‡GC2b	H	OSO_3^-	H	SB	OH	*G. catenatum*	[85]
‡GC3b	H	H	H	SB	OH	*G. catenatum*	[85]
‡GC4b	OH	H	OSO_3^-	SB	OH	*G. catenatum*	[85]
‡GC5b	OH	OSO_3^-	H	SB	OH	*G. catenatum*	[85]
‡GC6b	OH	H	H	SB	OH	*G. catenatum*	[85]
Other PST Analogs							
M1	H	OH	H	$OCONHSO_3^-$	OH	Metabolic transformation	[56,81]
M2	H	OH	H	$OCONH_2$	OH	Metabolic transformation	[56]
M3	H	OH	OH	$OCONHSO_3^-$	OH	Metabolic transformation	[56]
M4	H	OH	OH	$OCONH_2$	OH	Metabolic transformation	[56]
*M5						Metabolic transformation	[56]

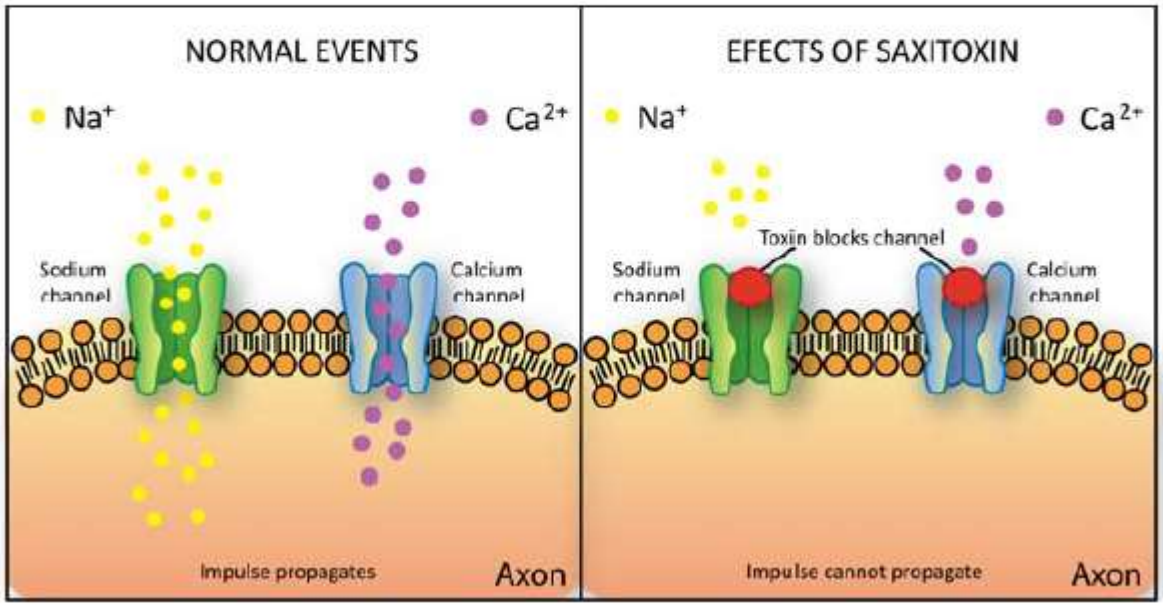
Table 1. *Cont.*

Toxin	R1	R2	R3	^n^R4	R5	Origin	Ref.
Other PST Analogs							
*A						Unknown	[86]
*B						Unknown	[86]
*C						Unknown	[86]
*D						Unknown	[86]
SEA	H	$CCOO^-$	H	$OCONH_2$	OH	*Atergatis floridus*	[87]
STX-uk	H	H	H	$OCONHCH_3$	OH	*Tetraodon cutcutia*	[88]
Zetekitoxin AB						*Atelopus zeteki*	[89]

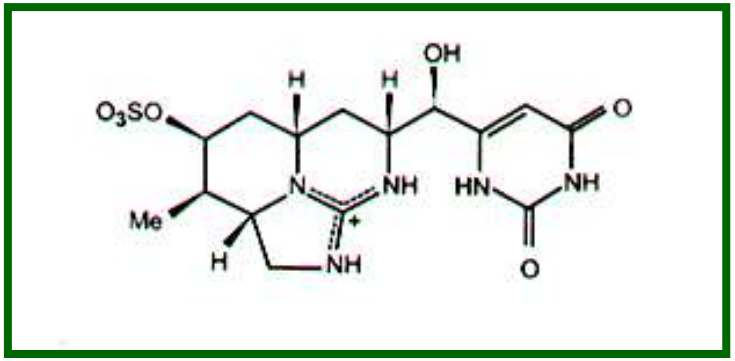
Wiese et al 2010

MECANISMO DE AÇÃO: STX e neoSTX

Figure 7. Schematic representation of saxitoxin toxicity mechanism. Saxitoxin binds to the sodium or calcium channels of the nerve axon membranes, preventing the passage of these ions through the cell membrane thus blocking the transfer of the nerve impulse.



Valerio et al (2010)



CILINDROSPERMOPSINA:

1. Alcalóide citotóxico (Fígado, rins, timo, coração e células correlatas)
2. Inibidor de síntese protéica (Terao et al, 1994; Froscio et al., 2003)
3. Mutagênico e potencialmente carcinogênico (Humpage et al., 2000; Shen et al., 2002)
4. Possível atividade neurotóxica (Kiss et al., 2002)
5. Disruptor endócrino (Young et al., 2008)

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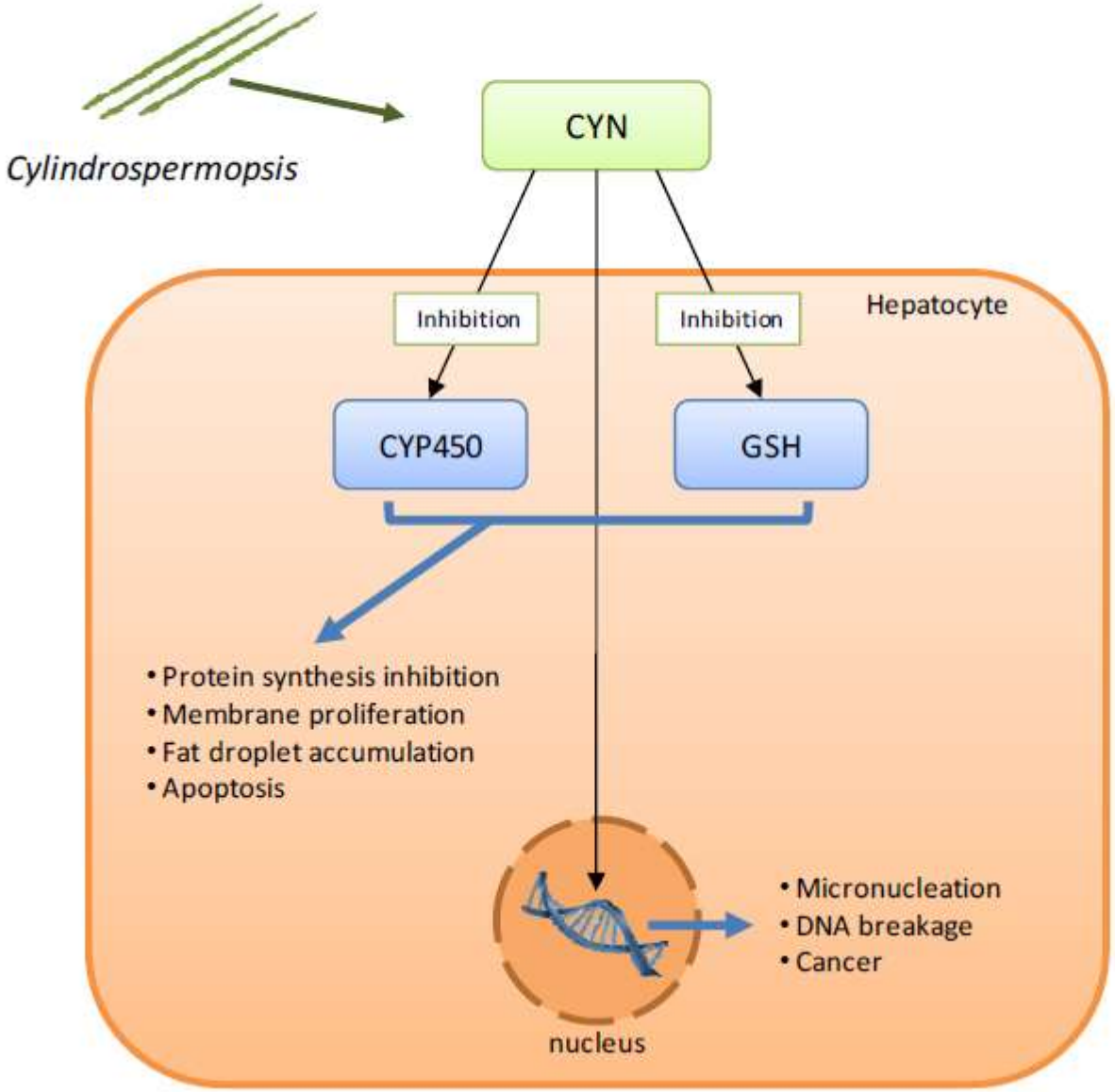
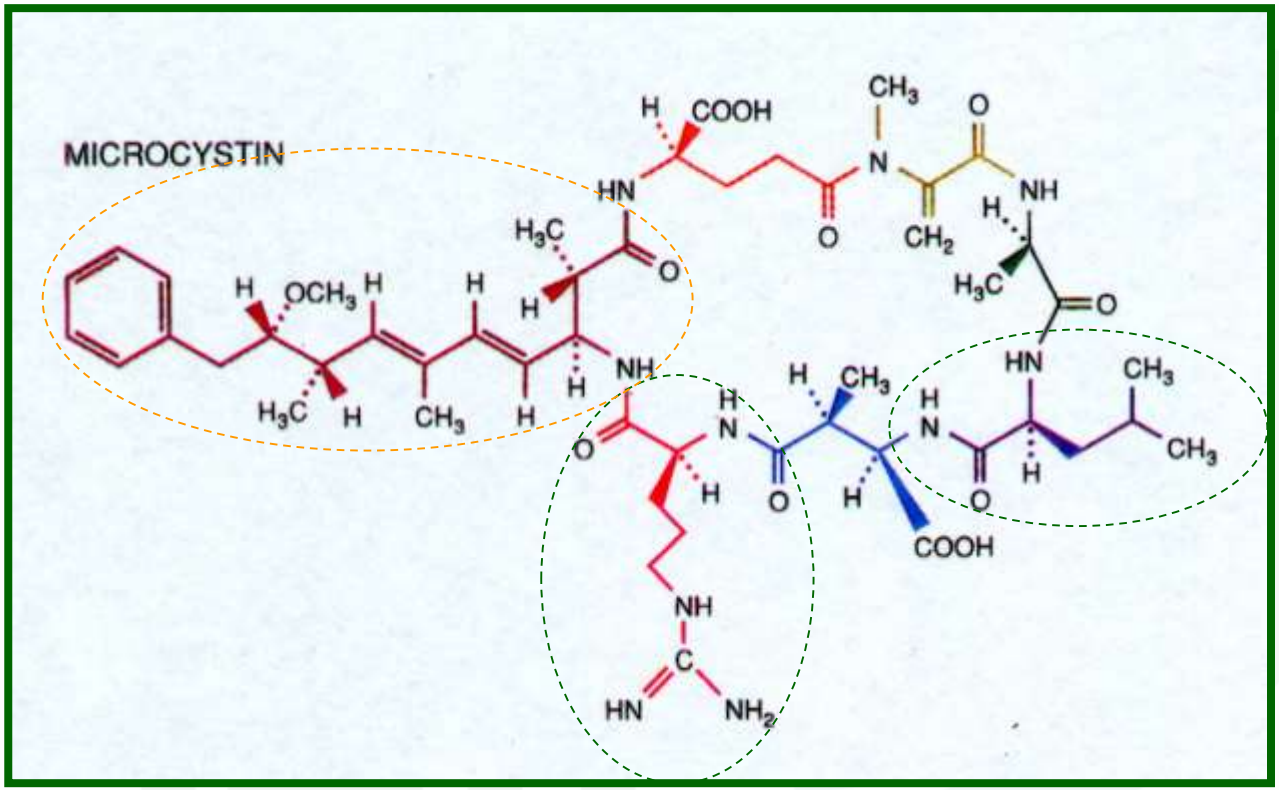
Figure 4. Schematic representation of the known molecular mechanisms involved in Cylindrospermopsin (CYN) toxicity. There is inhibition of glutathione (GSH) and protein synthesis, as well as cytochrome P450 (CYP450), and CYN interaction with DNA.



Valerio et al (2010)

MICROCISTINAS



São consideradas carcinogênicas pelo mecanismo de ação e por dados, tanto de estudos em animais como por dados epidemiológicos

http://figshare.com/articles/_Microcystin_congeners_described_in_the_literature/880756

This list **aims at being the most comprehensive list of published microcystins** available.
If you find some microcystins missing, **please contribute** (timo.niedermeyer@uni-tuebingen.de)!

It is maintained at figshare: http://dx.doi.org/10.6084/m9.figshare.880756

I am aware that several more microcystins are mentioned in the literature. In this compilation, hoewever, only MCs are listed where structure elucidation has been more or less convincing. Tentative "well, we think it might posssibly be" does not justify inclusion in this list.
((Tandem-)MS and at least some NMR data mandatory)

Current contributors: Timo H. J. Niedermeyer
Date of last update: 12.06.2014

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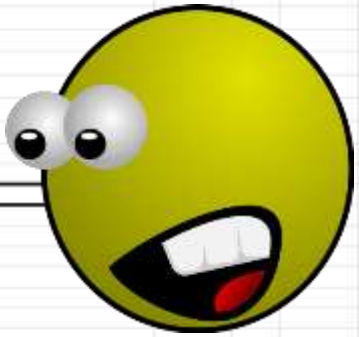
A remark on the configuration: If not otherwise 6 is D-iso- and 7 is D-
Feel free to play with the evaluation pivot table ADMAdda in position 5? ;-)
I have sorted the MCs acco to their Mr, bu have fun!

	1	2
24	1	2
25	Ala	Leu
26	Ala	Leu
27	Ala	Leu
28	Ala	Leu



1	3	4	5	6	7	MC name	Genus	Mr	Author	Year	Journal	Pages	counts	added
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Ala	Leu	MeAsp	Ala	Adda	Glu	Mdha	LA	Microcystis	909	Botes	1984	Journal of the Chemical Society, Perkin Transactions I	2311-2318	20/09/2012
Ala	Leu	Asp	Aba	Adda	Glu(OCH3)	Mdha	Asp3Glu(OCH3)6-LAba	Microcystis	923	del Campo	2010	Environmental Pollution	2906-2914	20/09/2012
Ala	Leu	MeAsp	Aba	Adda	Glu	Mdha	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]nal of Chromatography	435-440	20/09/2012
Ala	Leu	MeAsp	Val	Adda	Glu	M[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]con	1541-1549	20/09/2012
Ala	Leu	Asp	Leu	Adda	Glu	M[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]lytical Chemistry	501-512	20/09/2012
Ala	Phe	MeAsp	Ala	Adda	Glu	M[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]ischemistry Letters	575-581	11/06/2014
Ala	Leu	MeAsp	Leu	Adda	Glu	M[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]con	1541-1549	20/09/2012
Ala	Ala	MeAsp	Arg	Adda	[illegible]	M[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]nal of Organic Chemistry	866-872	20/09/2012
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Ala	Leu	Asp	Arg	[illegible]	Glu	D[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]con	479-489	20/09/2012
Ala	Leu	MeAsp	Met	[illegible]	Glu	M[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]con	1541-1549	20/09/2012
Ala	Glu	Asp	[illegible]	Adda	Glu	Dha	Asp3Dha7-EE(OMe)	Anabaena	969	Namikoshi	1998	Chemical Research in Toxicology	143-149	20/09/2012
Ala	Val	MeAsp	[illegible]	Adda	Glu	Mdha	VF	Microcystis	971	Bateman	1995	Journal of Chromatography A	253-268	20/09/2012

published microcystins | evaluation pivot table - MCs | published nodularins | evaluation pivot table - NODs | Literature Microcystins | Litera

published microcystins

120	Adda
121	Adda
122	Adda
123	ADMAdda
124	Adda
125	Adda

Ala	Hty	MeAsp	Arg	Adda	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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Ala	Hty	Asp	Tyr	Adda	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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Ala	Leu	MeAsp	Arg	Adda	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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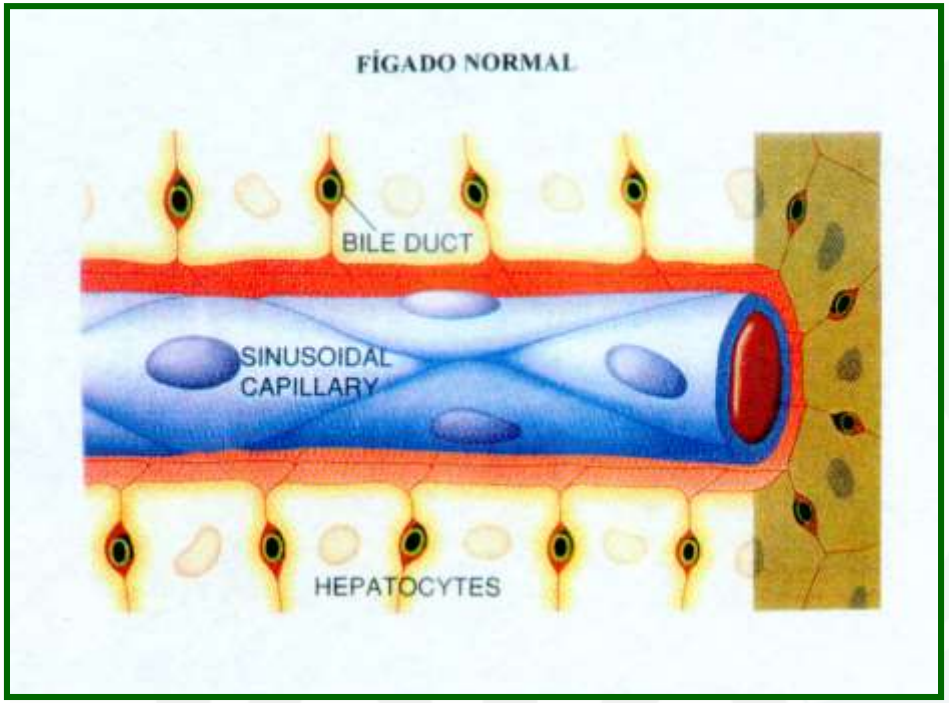
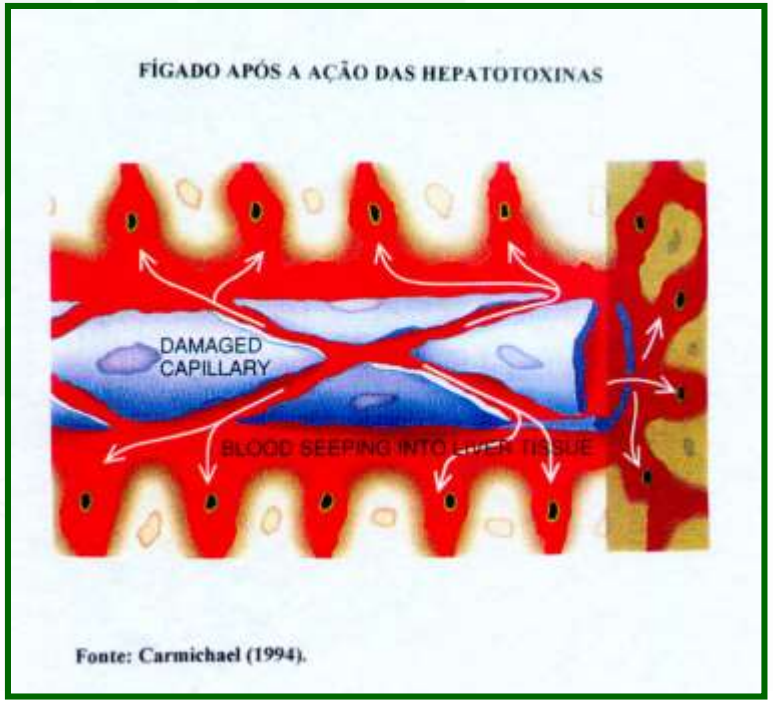
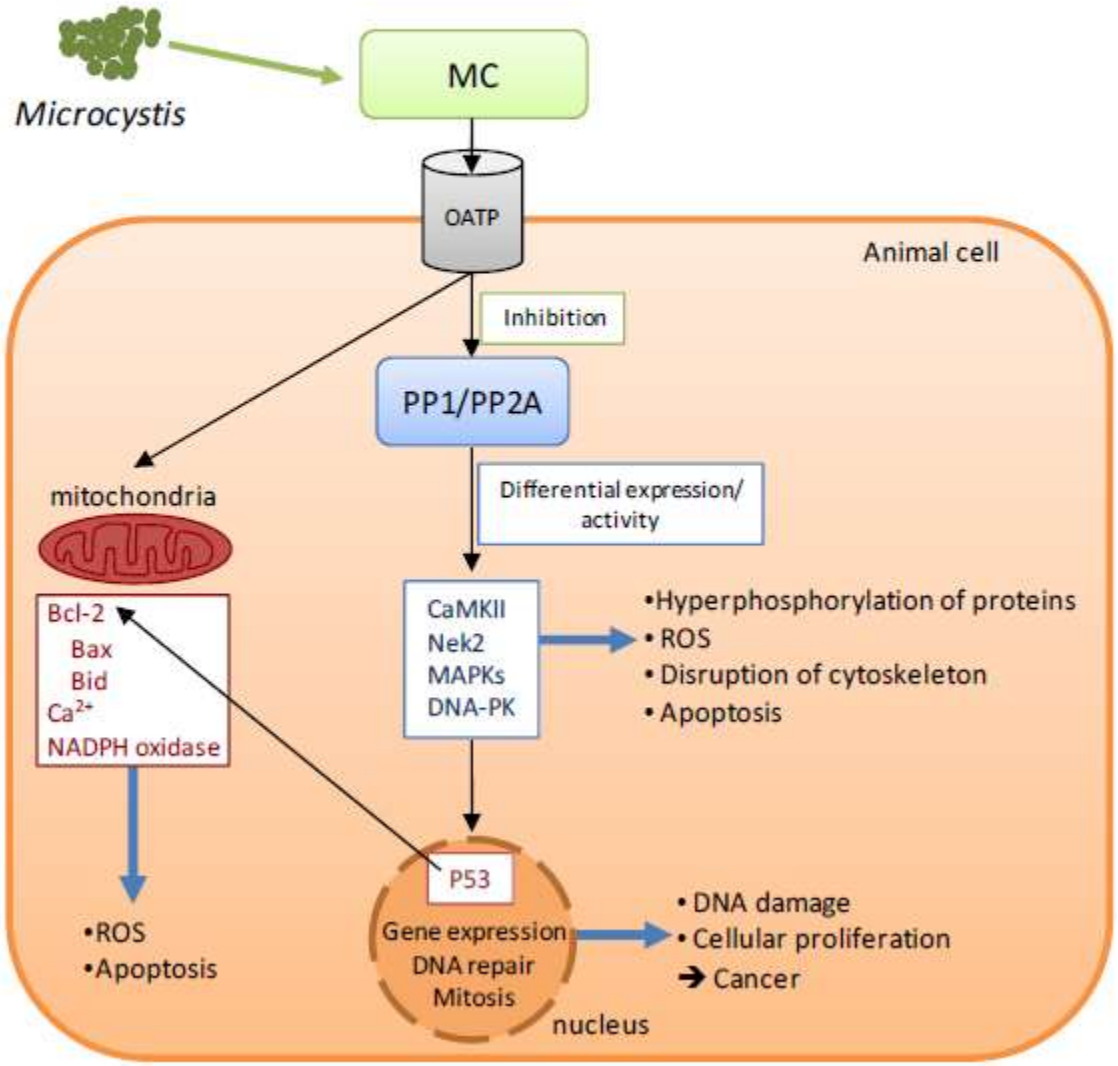
MECANISMO DE AÇÃO: MICROCISTINAS





Carmichael, 1994

Figure 2. Schematic representation of the molecular mechanisms of microcystins (MC) toxicity. After intake through the plasma membrane by the organic anion transporting polypeptide system (OATP), MC binds specifically to the serine/threonine protein phosphatases (PP1/PP2A), inhibiting them and leading to a cascade of events responsible for the MC cytotoxic and genotoxic effects in animal cells (see text for details).



Valerio et al (2010)

TOXINA	ESPÉCIE	ORGANISMO	DL_{50} ($\mu g\ Kg^{-1}$)
Botulina	*Clostridium botulinum*	bactéria	0,00003
Toxina tetânica	*Clostridium tetani*	bactéria	0,001
Maitotoxina (MTX)	*Gambierdiscus*	Dinoflagelado	0,05 (Murata et al 1993)
Toxina da difteria	*Corynebacterium diphytheriae*	bactéria	0,3
Saxitoxina	*Aphanizomenon flos-aquae*	cianobactéria	10
	Cylindrospermopsis raciborskii		
Toxina de cobra	*Naja naja*	cobra	20
Anatoxina-a(s)	*Anabaena flos-aquae*	cianobactéria	20
Nodularina	*Nodularia spumigena*	cianobactéria	50
Microcistina	*Microcystis aeruginosa*	cianobactéria	50-1200
Anatoxina-a	*Anabaena flos-aquae*	cianobactéria	200
Estricnina	*Strychnos mux-vomica*	planta	200
Curare	*Chondrodendron tomentosum*	Planta	500

Laboratório de Ecofisiologia e Toxicologia de Cianobactérias

- **Exposição: risco para saúde**
  incidentes com animais

- **Intoxicação e morte humana**

letc
Laboratório de Ecofisiologia e Toxicologia de Cianobactérias

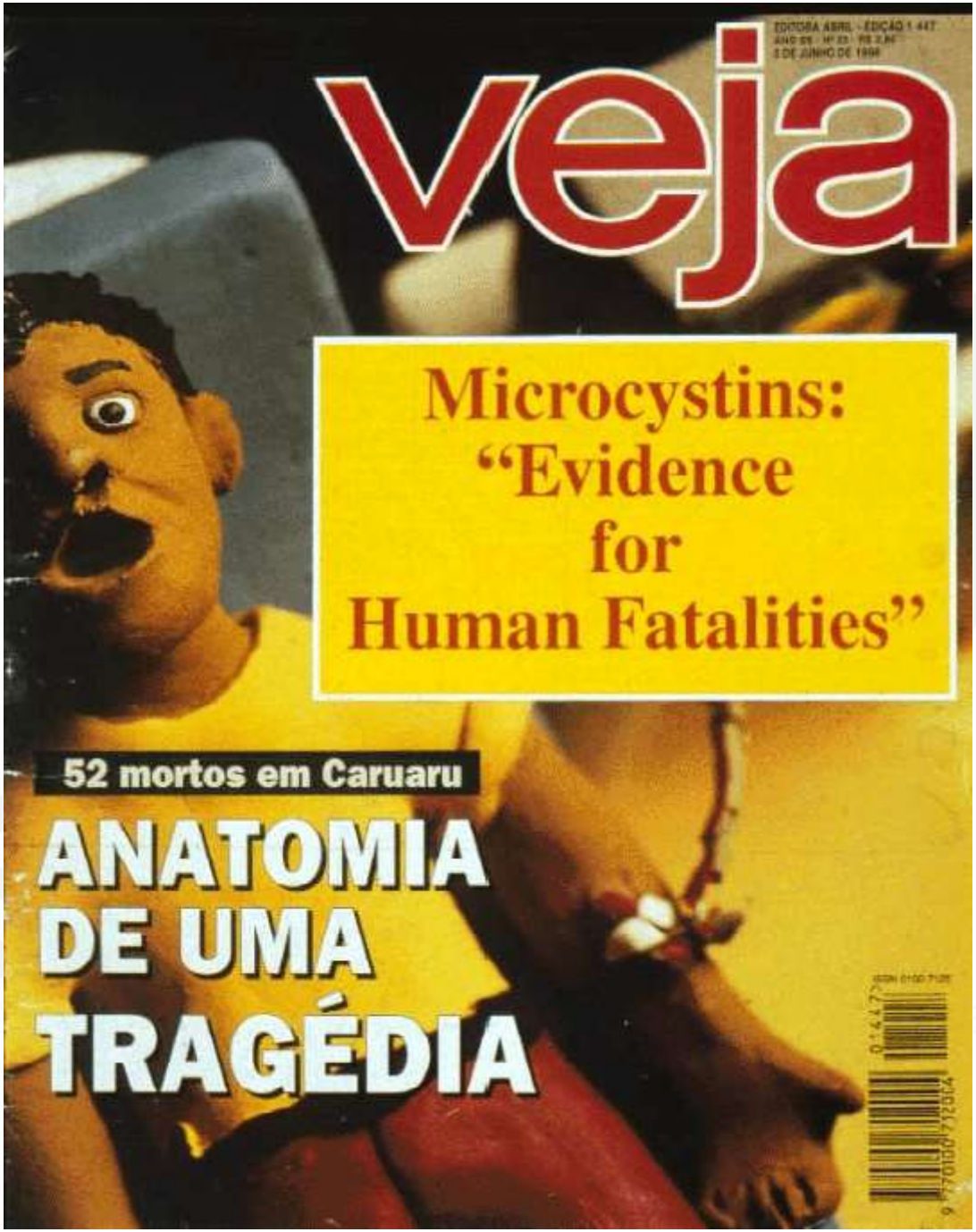
Casos de intoxicação Humana

Itaparica – Bahia: 1988

- Enchimento da represa de Itaparica
- Floração de Anabaena e Microcystis
- Ocorrência de 2000 casos de gastroenterite ao longo de 42 dias
- 88 mortes – maioria crianças

ietc
Laboratório de Ecofisiologia e Toxicologia de Cianobactérias

Teixeira et al, 1993


veja
Microcystins:
"Evidence
for
Human Fatalities"
52 mortos em Caruaru
ANATOMIA
DE UMA
TRAGÉDIA

Fevereiro – 1996:

117 de 136 pacientes (86%) dialisados passaram a apresentar os seguintes :

- ✓ Dor de cabeça, distúrbios visuais, náusea e vômito.
- ✓ Hepatomegalia

60 mortes ocorridas até outubro – 1996 puderam ser atribuídas a uma mesma síndrome

Sistema de purificação de água na clínica

Concentrações de Microcistina e Cilindrospermopsina no carvão ativado, resinas de troca iônica e areia das clínicas A e B, em Caruaru

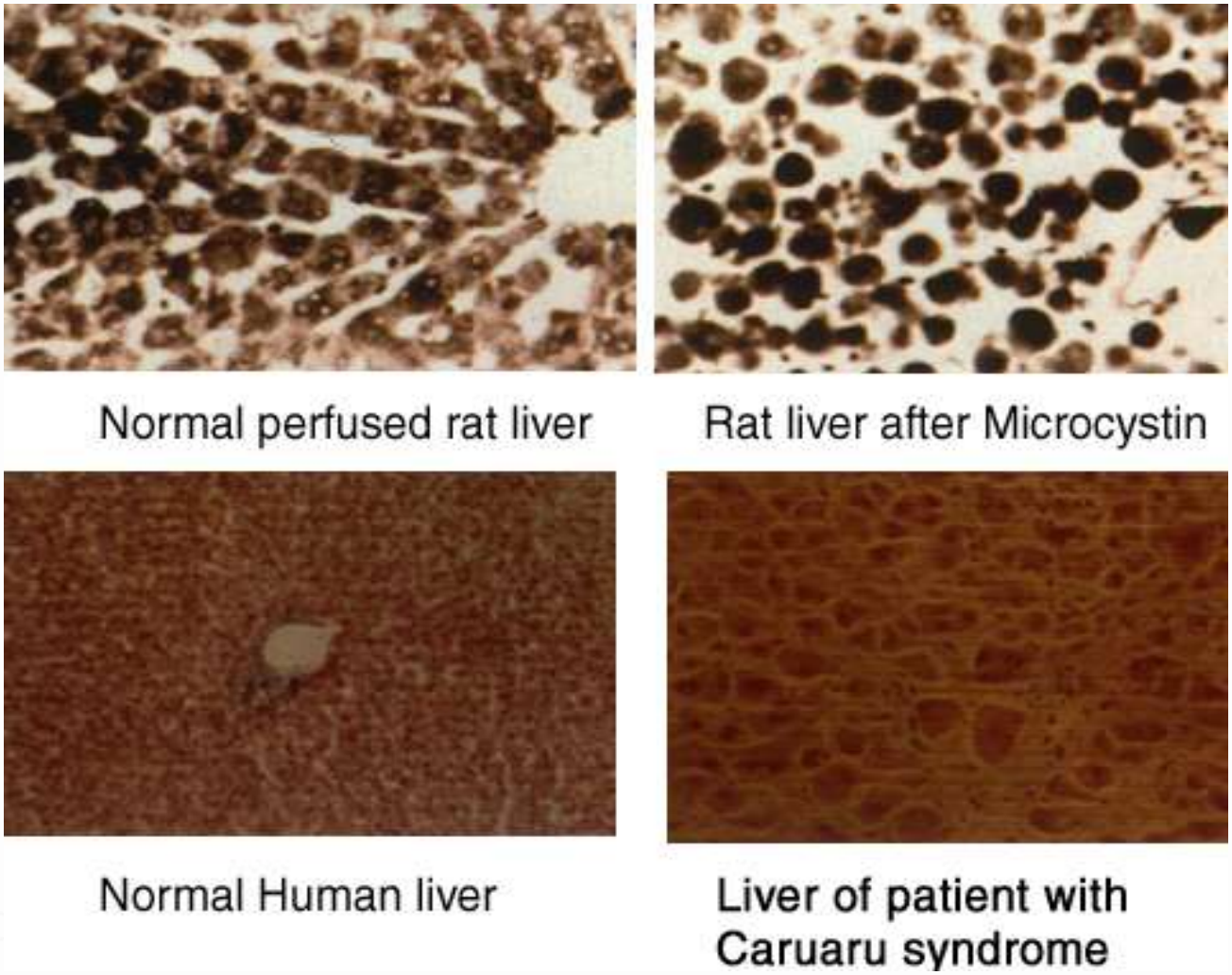
Table 2. Microcystin (by ELISA) and cylindrospermopsin (by LC/MS/MS) content of carbon, ion-exchange resin, and sand filters from dialysis centers A and B in Caruaru, Brazil.

Center/sample source	Microcystin (μg/g)	Cylindrospermopsin (μg/g)
Center A, carbon	1.0	19.70
Center A, anion resin	0.5	0.02
Center A, cation resin	2.1	0.05
Center A, sand	ND	ND
Center B, carbon	3.4	ND
Center B, sand	ND	ND

ND, not detected.

Laboratório de Ecofisiologia e Toxicologia de Cianobactérias

Carmichael et al (2001)



Azevedo et al (2002)

OMS – "Toxic cyanobacteria in water. A guide to their public health consequences, monitoring and management" (Chorus e Bartram, 1999)

RECOMENDA

- ✓ **Nível máximo aceitável para consumo oral**

Equivalentes de microcistinas = 1µg.L^{-1}.dia

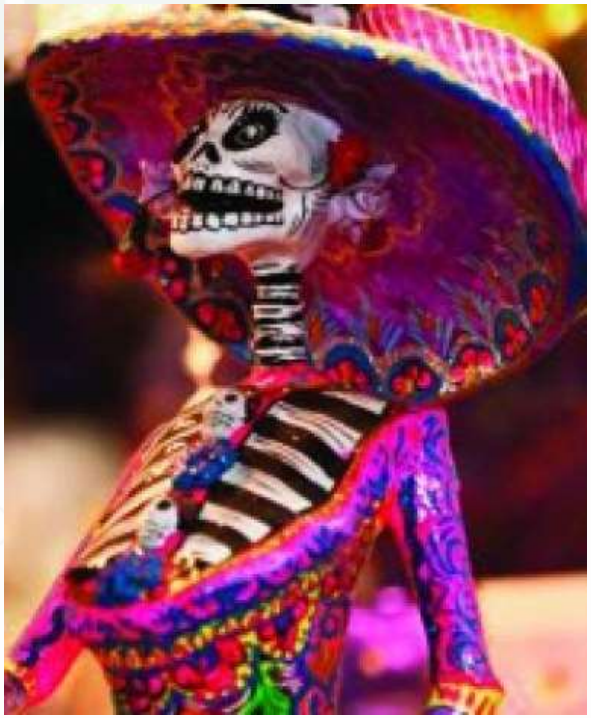
Equivalentes de cilindrospermopsina = 1,0 µg.L^{-1}

Equivalentes de saxitoxinas = 3,0 µg.L^{-1}

Ingestão diária tolerada (TDI) = 0,04µg.Kg^{-1}.dia^{-1}

Nova legislação – PORTARIA Nº 2.914, DE 12 de dezembro DE 2011

modificações:

- ✓ **STX mandatória**
- ✓ **CYN contunuará como recomendada porém o limite proposto é de 1µg/L (Humpage & Falconer 2003)**
- ✓ **Se as concentrações das cianotoxinas excederem o máximo estabelecido para água tratada, analises de cianotoxinas deverão ser realizadas**

Gracias