Developing Cyanotoxin Action Levels for Humans and Domestic Animals

January, 2013

Regina Linville, Ph.D.

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

TOXICOLOGICAL SUMMARY AND SUGGESTED ACTION LEVELS TO REDUCE POTENTIAL ADVERSE HEALTH EFFECTS OF SIX CYANOTOXINS

May 2012

Ned Butler, Ph.D.
Jim Carlisle, D.V.M., M.Sc.
Regina Linville, Ph.D.

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

http://www.waterboards.ca.gov/water_issues/programs/peer_review/peer_review_cyanotoxins.shtml

Developing Action Levels

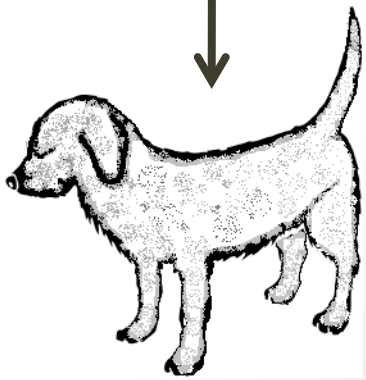
- **Cyanotoxins considered**: anatoxin-a, cylindrospermopsin, microcystin-LR, -RR, -YR and -LA
- **Reference doses** developed for humans and animals
- **Exposure scenarios** estimated for humans and animals
- **Action levels** derived for humans and animals in several types of exposure media

Overview of the Process

Reference Dose
Maximum recommended dose

Exposure
Amount of media consumed (e.g., water)

Action Level
Health-protective chemical concentration in media (e.g., mg/L)



Reference Dose

The Reference Dose (RfD): level of exposure over a given time period that is not expected to cause any adverse effects

1. Identify the best dose-response study
2. Identify a dose that effects very few test animals
3. Translate that animal dose to humans and domestic animals using Uncertainty Factors

Reference Dose Studies

Test Animal and Endpoint

	Type RfD	MCs	ANA-a	CYN
Human	Acute	Rat Liver Tox	Mouse Neurotox	
	Sub-chronic	Rat Liver Tox	Rat Neurotox	Mouse Kidney Tox
	Chronic	Mouse Histo		
Domestic Animal	Acute	Sheep Lethality	Mouse Lethality	Rat Lethality
	Sub-chronic	Rat Liver Tox	Mouse Lethality	Mouse Kidney Tox

Uncertainty Factors

RfD = “No Effect Level” UF

Human cumulative UF of 1000: “mouse to man” (10); sensitive people (10); incomplete data (10)

Domestic Animal UF of 100 (acute) to 10 (subchronic): interspecies extrapolation; incomplete data; severity of endpoint (acute)

Domestic Animal *exposure* UF of 3 was also applied due to the preferential consumption of cyanobacteria. In this case, estimated exposure was multiplied by 3

“No Effect Level” ÷ UF = RfD

	Type RfD	MCs	ANA-a	CYN
Human (mg/kg-d)	Acute	0.0064 0.0000064	2.5 0.0025	
	Sub-chronic	0.0064 0.0000064	0.5 0.0005	0.033 0.000033
	Chronic	0.003 0.000003		
Domestic Animal (mg/kg-d)	Acute	3.7 0.037	2.5 0.025	4.0 0.04
	Sub-chronic	0.0064 0.00064	*Use Acute*	0.033 0.0033

Estimating Exposures

Swimmers receiving highest exposure per body weight are children 7-10 years old

Fishers assessed as adults eating one meal of contaminated sport fish or shellfish per week

Cattle with highest exposure are lactating dairy cows consuming water or crusts at levels predicted using agricultural guidance.

Dog exposure was estimated for drinking and eating crusts using veterinary guidance and professional judgment.

Swimmers

	Exposure Routes Considered			
	Ingestion	Inhalation	Dermal	Total[a]
MCs	√			121
CYN	√			121
ANA-a	√	√	√	37.2

[a] $\text{Total Dose} = \dfrac{1}{\text{Ingestion} + \text{Inhalation} + \text{Dermal}}$

$$\frac{\text{Rec. water conc. (mg/L)}}{\text{Swimmer dose (mg/kg} \cdot \text{d)}} \times \text{RfD (mg/kg} \cdot \text{d)} = \text{Action level (mg/L)}$$

Fishers

Based on consumption of sportfish and shellfish by the general fishing population

$$D_{consume} = \frac{C_F \times CR}{BW} \qquad C_F = \frac{RfD \ x \ BW}{CR}$$

Set $D_{consume}$ equal to RfD and solve for C_F

$D_{consume}$ = Dose to fisher (should meet RfD)

C_F = Concentration in fish (Action Level)

CR = Consumption rate (1 meal/wk, 8oz fresh)

BW = Body weight of fisher (70 kg Adult)

Revisiting Uncertainty for Animals

- **Advised by peer reviewers** to address:
  - Preferential consumption of cyanobacteria
  - Uncertainty in exposure via grooming

- **Uncertainty factor of 3** was applied to each domestic animal exposure scenario
  - Consumption may be up to 3 times higher than estimated
  - **Estimated intake * 3 = Final Exposure**

Domestic Animals

$$C_x = \frac{RfD \times BW}{IR \times UF}$$

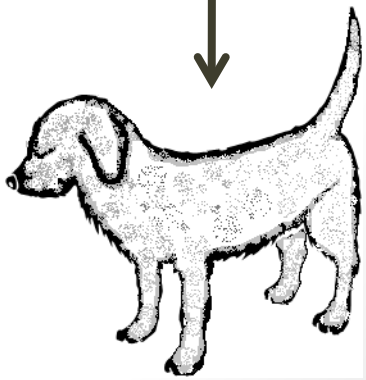
- C_x = Concentration of cyanotoxin in water or crusts (Action Level)
- RfD = Reference dose (acute or subchronic)
- BW = Body weight (cattle or dog)
- IR = Intake rate (of water or crusts by cattle or dog)
- UF = Uncertainty factor of 3

Overview of the Process

Reference Dose
Maximum recommended dose

Exposure
Amount of media consumed (e.g., water)

Action Level
Health-protective chemical concentration in media (e.g., mg/L)



Action Level

Health-protective chemical concentrations in the environmental media that are designed to prevent an organism from receiving exposures above the RfDs

- Risk management tool
- Not criteria or regulation
- Not applicable to human drinking water exposures

Action Levels for Humans Subchronic Exposure

	MCs[1]	ANA-a	CYN	Media (units)
Recreational Uses[2]	0.8	90	4	Water (µg/L)
Sport Fish Consumption	10	5000	70	Fish (ng/g) ww[3]

[1] Includes microcystins LA, LR, RR, and YR

[2] Not for drinking water

[3] Wet weight or fresh weight

Action Levels for Dogs & Cattle Subchronic and Acute Exposure

	MCs[1]	ANA-a	CYN	Media (units)
Dogs Water Intake	2 100	100 100	10 200	Water (µg/L)
Cattle Water Intake	0.9 50	40 40	5 60	Water (µg/L)
Dogs Crusts & Mats	0.01 0.5	0.3 0.3	0.04 0.5	Crusts/Mats (mg/kg) dw[2]
Cattle Crusts & Mats	0.1 5	3 3	0.4 5	Crusts/Mats (mg/kg) dw[2]

[1] Includes MCs LA, LR, RR, and YR; [2] Dry sample weight

Limiting Subchronic Action Levels for Recreational Waters

	MCs[1]	ANA-a	CYN	Media (units)
Human Swimming	**0.8**	90	**4**	Water (µg/L)
Dog Drinking	2	100	10	Water (µg/L)
Cattle Drinking	0.9	**40**	5	Water (µg/L)

[1] Includes microcystins LA, LR, RR, and YR