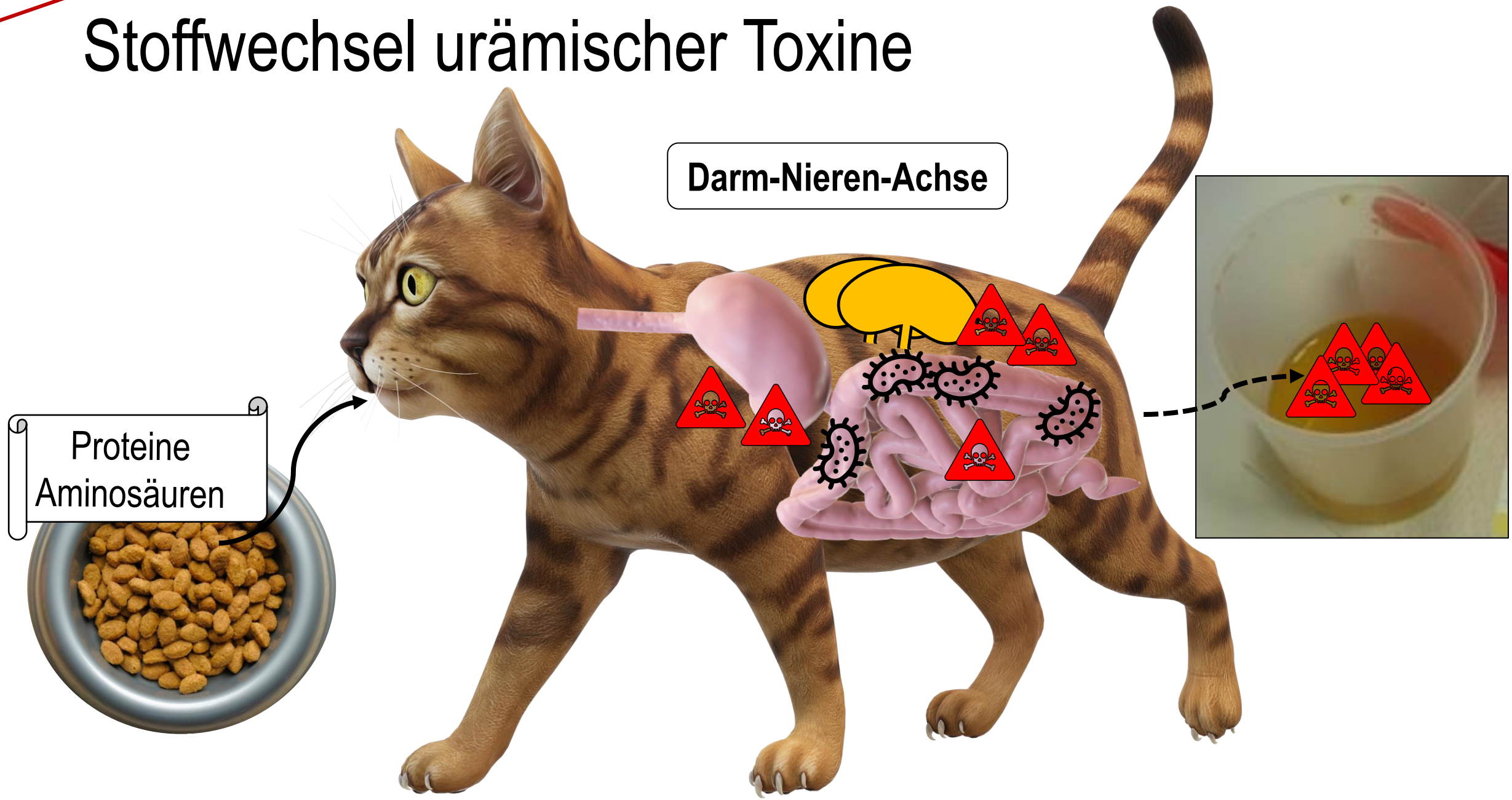
Urämische Toxine bei der Katze
Auswirkungen und Therapieoptionen

KLEINTIER
KLINIK
ETTLINGEN

Februar 2023

Dorothee Dahlem

Stoffwechsel urämischer Toxine



Urämische Toxine

Bestandteile organischer Verbindungen

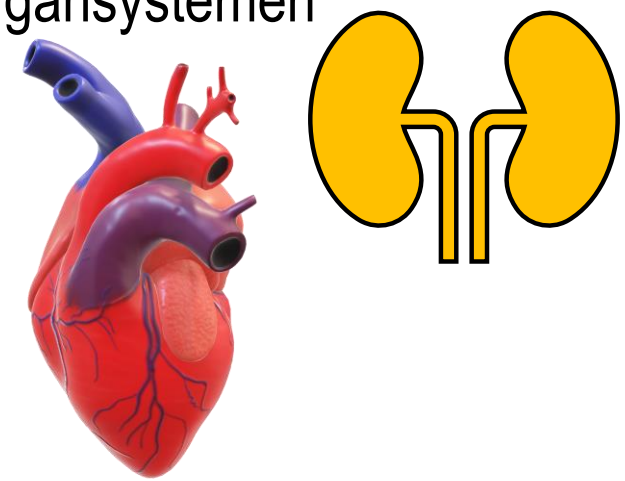
Elimination nur eingeschränkt möglich

↓

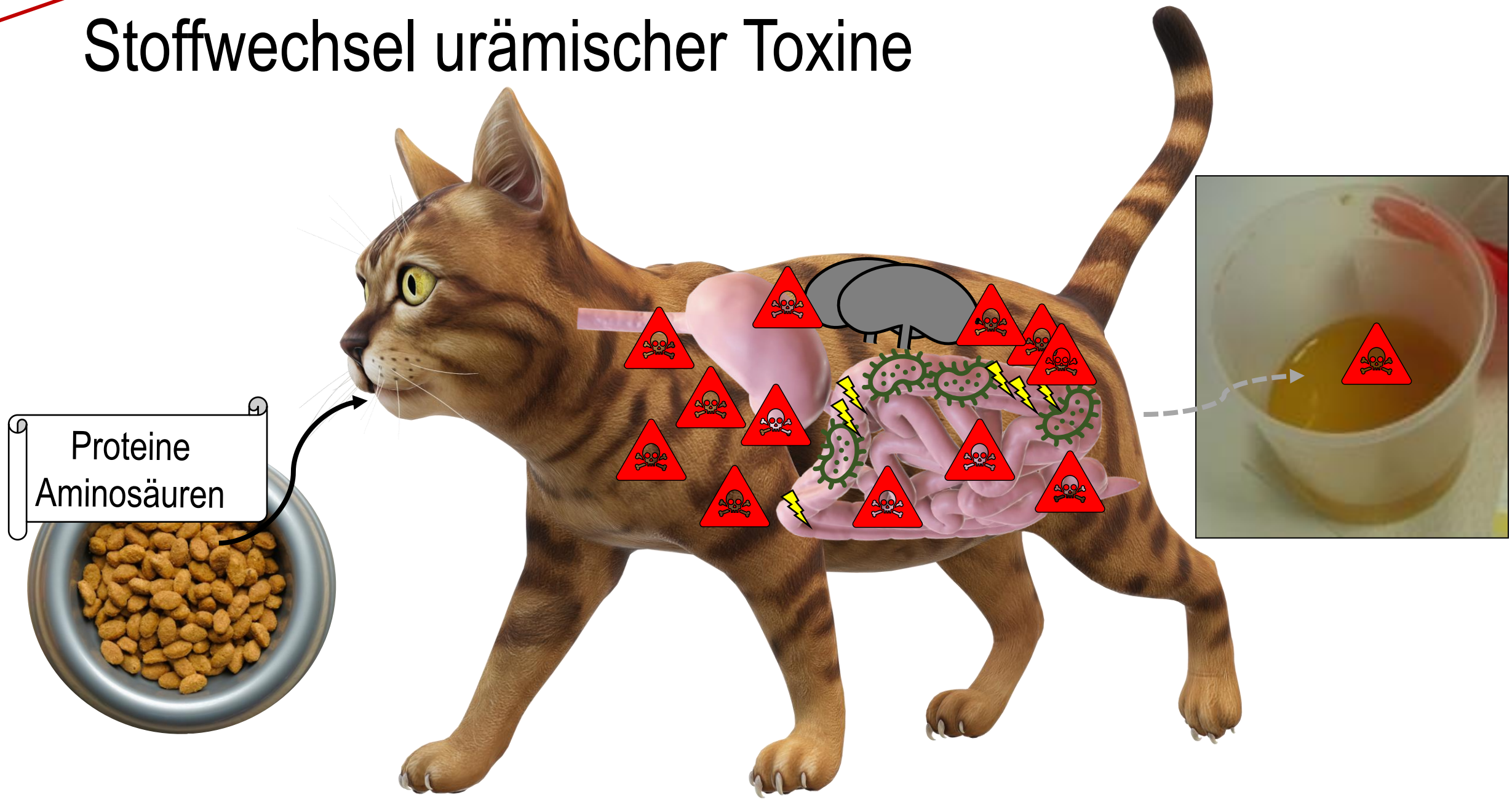
Akkumulation im vaskulären System

↓

Affinität zu spezifischen Organsystemen

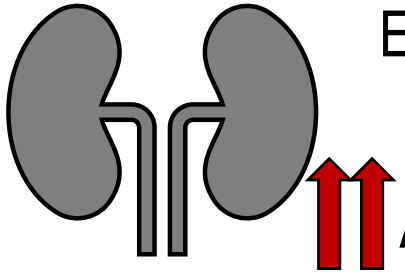


Stoffwechsel urämischer Toxine



Urämische Toxine

Bestandteile organischer Verbindungen



Elimination nur eingeschränkt möglich

↓

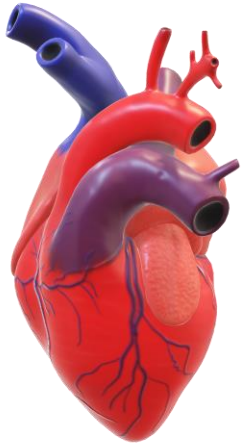
Akkumulation im vaskulären System

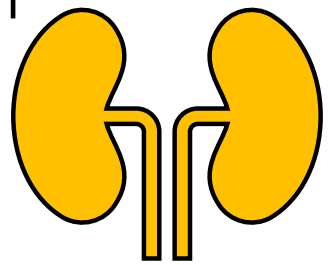
↓

Affinität zu spezifischen Organsystemen

↙

Urämisches Syndrom





Urämische Toxine - Klassifikationskriterien

1. Chemische Identifikation und Charakterisierung
2. Quantitative Analyse des Toxins in biologischen Flüssigkeiten
3. ↑Konzentration des Toxins während Urämie
4. Verbindung zwischen Toxinkonzentration und mindestens einer Manifestation der Urämie
5. ↓Konzentrationsabfall des Toxins => Verbesserung der urämischen Manifestation

Glassock RJ. Uremic toxins: what are they? An integrated overview of pathobiology and classification. J Ren Nutr. 2007;18:2-6.

OUR WORK GROUP

EUTox is a working group of the „European Society of Artificial Organs" (ESAO). The EUTox working group is composed of twenty six academic and seven industrial members. The topic of the EUTox working group is the identification of yet unknown uremic toxins, the characterisation of uremic toxins and the development of new therapeutic approaches for the treatment of chronic kidney diseases.

Vanholder R et al. Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003;63:1934-1943.

NAME	CLASS	NORMAL CONCENTRATION (AVERAGE)	UREMIC CONCENTRATION (AVERAGE)	RELATIVE INCREASE	PATHOLOGICAL ASSOCIATIONS
1-Methyladenosine	water-soluble	17.10 (+/-5.10) µg/L, [n=10]	104.00 (+/-56.20) µg/L, [n=17]	6.08	Oncologic [3] Hematologic [1] Cardiovascular [1]
1-Methylguanosine	water-soluble	13.70 (+/-16.90) µg/L, [n=10]	41.60 (+/-23.80) µg/L, [n=17]	3.04	unknown [1]
1-Methylinosine	water-soluble	13.50 (+/-3.90) µg/L, [n=10]	620.40 (+/-203.40) µg/L, [n=14]	45.96	
2-Heptenal	water-soluble	17.70 (+/-5.33) µg/L, [n=20]	54.66 (+/-33.49) µg/L, [n=17]	3.09	
2-Hexenal	water-soluble	22.05 (+/-6.56) µg/L, [n=20]	61.74 (+/-20.48) µg/L, [n=17]	2.80	
2-Nonenal	water-soluble	18.48 (+/-5.17) µg/L, [n=20]	101.78 (+/-58.38) µg/L, [n=17]	5.51	
2-Octenal	water-soluble	26.08 (+/-16.38) µg/L, [n=20]	32.51 (+/-21.16) µg/L, [n=17]	1.25	
3-Carboxy-4-Methyl-5-Propyl-2-Furanpropanoic Acid (CMPF)	protein-bound	4.60 (+/-1.80) (3.61-7.70) mg/L, [n=29], p=0.00, D:**A**	25.95 (+/-10.23) (3.70-94.00) mg/L, [n=63], p=0.00, D:**C**	5.64	
3-Deoxyglucosone	protein-bound	0.30 (+/-0.10) mg/L, [n=30]	1.70 (+/-1.00) mg/L, [n=27]	5.67	
4-Decenal	water-soluble	15.86 (+/-5.25) µg/L, [n=20]	53.90 (+/-26.80) µg/L, [n=20]	3.40	
4-HO-Decenal	water-soluble	10.25 (+/-7.12) µg/L, [n=20]	36.55 (+/-22.27) µg/L, [n=17]	3.57	
4-HO-Hexenal	water-soluble	25.08 (+/-9.87) µg/L, [n=20]	63.84 (+/-25.31) µg/L, [n=17]	2.55	
4-HO-Nonenal	water-soluble	16.38 (+/-8.99) µg/L, [n=20]	117.31 (+/-47.74) µg/L, [n=17]	7.16	
4-HO-Octenal	water-soluble	10.65 (+/-3.56) µg/L, [n=20]	27.83 (+/-13.79) µg/L, [n=17]	2.61	
4-Pyridone-3-carboxamide-1-β-D-ribonucleoside	water-soluble	3.54 (+/-1.63) µg/L, [n=9]	156.12 (+/-169.18) µg/L, [n=11]	44.10	
8-Hydroxy-2'-deoxyguanosine	water-soluble	0.64 (+/-0.23) (0.20-1.26) µg/L, [n=85]	0.82 (+/-0.25) µg/L, [n=47]	1.28	
Adiponectin	middle		ng/L, [n=378], p=0.05, D:**A**	2.04	Cardiovascular [3] other [1] Endocrinology [1] Oncologic [1]
Adrenomedullin	middle		ng/L, [n=39], p=0.00, D:**B**	6.73	Cardiovascular [4]
Angiogenin	protein-b			2.61	
Arab(in)itol	water-soluble	0.37 (+/-0.12) (0.16-0.63) mg/L, [n=33], D:**B**	8.75 (+/-5.89) (0.80-15.00) mg/L, [n=28], D:**C**	23.64	
Argininic Acid	water-soluble	16.59 (+/-5.60) (16.59-77.00) µg/L, [n=16], D:**B**	65.82 (+/-33.36) (40.25-197.80) µg/L, [n=31], D:**B**	3.97	
Asymetric Dimethylarginine (ADMA)	water-soluble	0.15 (+/-0.08) (0.07-0.28) mg/L, [n=62], p=0.00, D:**B**	0.38 (+/-0.27) (0.10-7.30) mg/L, [n=220], p=0.00, D:**D**	2.60	Cardiovascular [2]
Atrial Natriuretic Peptide (ANP)	middle	27.88 (+/-10.09) (27.72-28.00) ng/L, [n=40], p=0.95, D:**A**	197.18 (+/-123.82) (187.88-202.00) ng/L, [n=41], p=0.80, D:**A**	7.07	Cardiovascular [1]
Basic fibroblast growth factor (BFGF)	middle	0.21 (+/-0.09) ng/L, [n=23]	1.35 (0.20-21.50) ng/L, [n=32]	6.43	
Calcitonin gene-related peptide (CGRP)	middle	185.66 (+/-11.37) ng/L, [n=20]	164.44 (+/-35.95) ng/L, [n=10]	0.89	
Cholecystokinin	middle	4.99 (+/-2.23) ng/L, [n=43]	26.06 (+/-22.91) (6.73-131.50) ng/L, [n=77], p=0.00, D:**C**	5.22	Nutrition [1]
Clara cell protein (CC16)	middle	0.01 (+/-0.01) mg/L, [n=117]	3.03 (+/-1.37) (2.80-12.50) mg/L, [n=26], p=0.50, D:**B**	218.04	
Complement Factor D	middle	1.90 (+/-0.50) mg/L, [n=5]	21.35 (+/-6.03) (11.40-27.70) mg/L, [n=37], p=0.00, D:**A**	11.23	
Creatine	water-soluble	9.70 (+/-3.30) mg/L, [n=24]	134.00 (+/-30.30) (?-235.80) mg/L, [n=29]	13.81	
Creatinine	water-soluble	9.68 (+/-0.24) (8.86-12.00) mg/L, [n=851], p=0.00, D:**A**	136.00 (+/-46.00) (?-240.00) mg/L, [n=19746]	14.04	Neurologic and CNS [1]
Cystatin C	middle	0.70 (+/-0.12) mg/L, [n=56]	11.13 (+/-4.48) (2.80-41.10) mg/L, [n=220], p=0.00, D:**C**	15.90	
Cytidine	water-soluble	468.00 µg/L, [n=1]	683.30 (+/-287.80) (?-1263.60) µg/L, [n=7]	1.46	
Decanal	water-soluble	17.16 (+/-4.95) µg/L, [n=20]	23.40 (+/-8.81) µg/L, [n=17]	1.36	
Degranulation Inhibiting Protein I	middle	321.70 (+/-59.70) µg/L, [n=23]	713.70 (+/-390.00) (?-1631.40) µg/L, [n=125]	2.22	
Delta-sleep Inducing Peptide	middle	0.90 (+/-0.29) µg/L, [n=12]	1.50 (+/-0.90) µg/L, [n=7]	1.67	
Dihydroxyphenylalanine (PB-DOPA)	protein-bound	6.60 (+/-0.73) mg/L, [n=21]	11.37 (+/-3.17) mg/L, [n=19]	1.72	Biochemical [1]
Dimethylamine	water-soluble	2.18 (+/-0.33) mg/L, [n=9]	10.32 (+/-1.55) mg/L, [n=7]	4.73	Nephrologic [1]
Dimethylglycine	water-soluble	381.10 µg/L, [n=33]	576.80 (?-1040.30) µg/L, [n=18]	1.51	
Endothelin	middle	20.80 (+/-3.80) ng/L, [n=23]	31.80 (+/-23.01) (3.00-63.00) ng/L, [n=25], p=0.00, D:**C**	1.53	Cardiovascular [1] Endocrinology [1]

Aktuell 130 urämische Toxine gelistet

Urämische Toxine - Klassifikation

Wasserlösliche Moleküle

<500 Da

Leicht entfernbar durch Hämodialyse

Beispiele: Harnstoff, Kreatinin

Proteingebundene Moleküle

Nur ungebundene Fraktion durch Dialyse entfernbar

Beispiele: Indole, Phenole

Moleküle mittlerer Größe

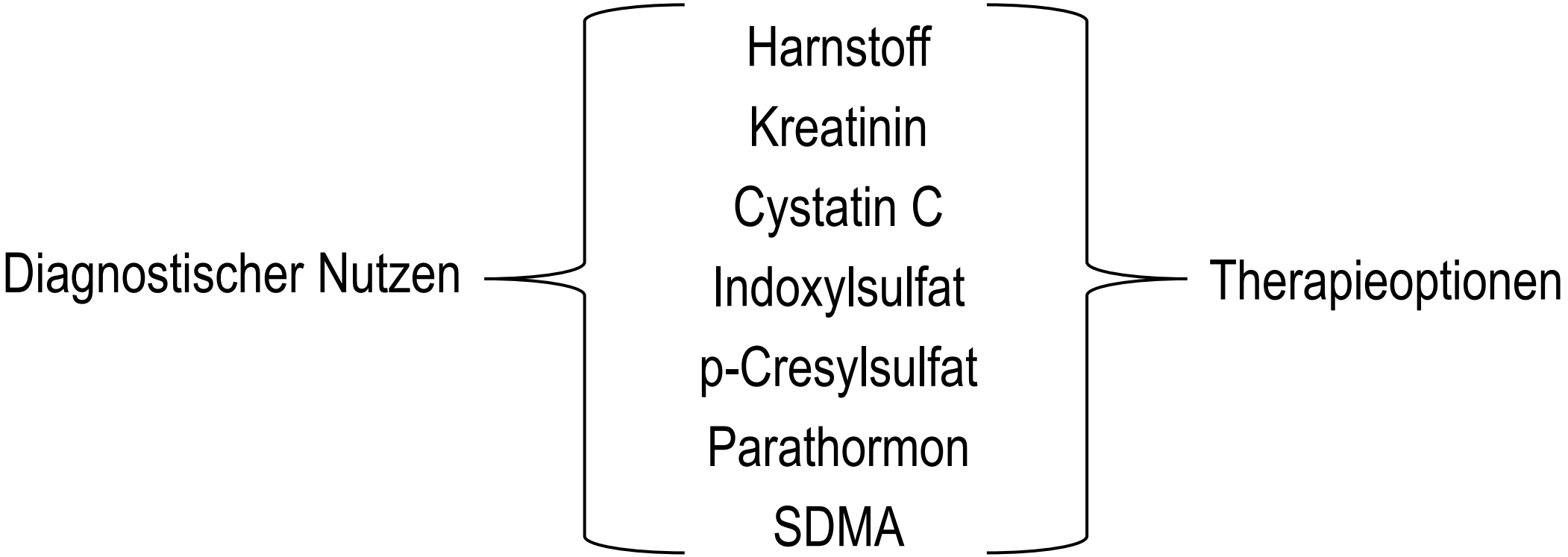
>500 Da

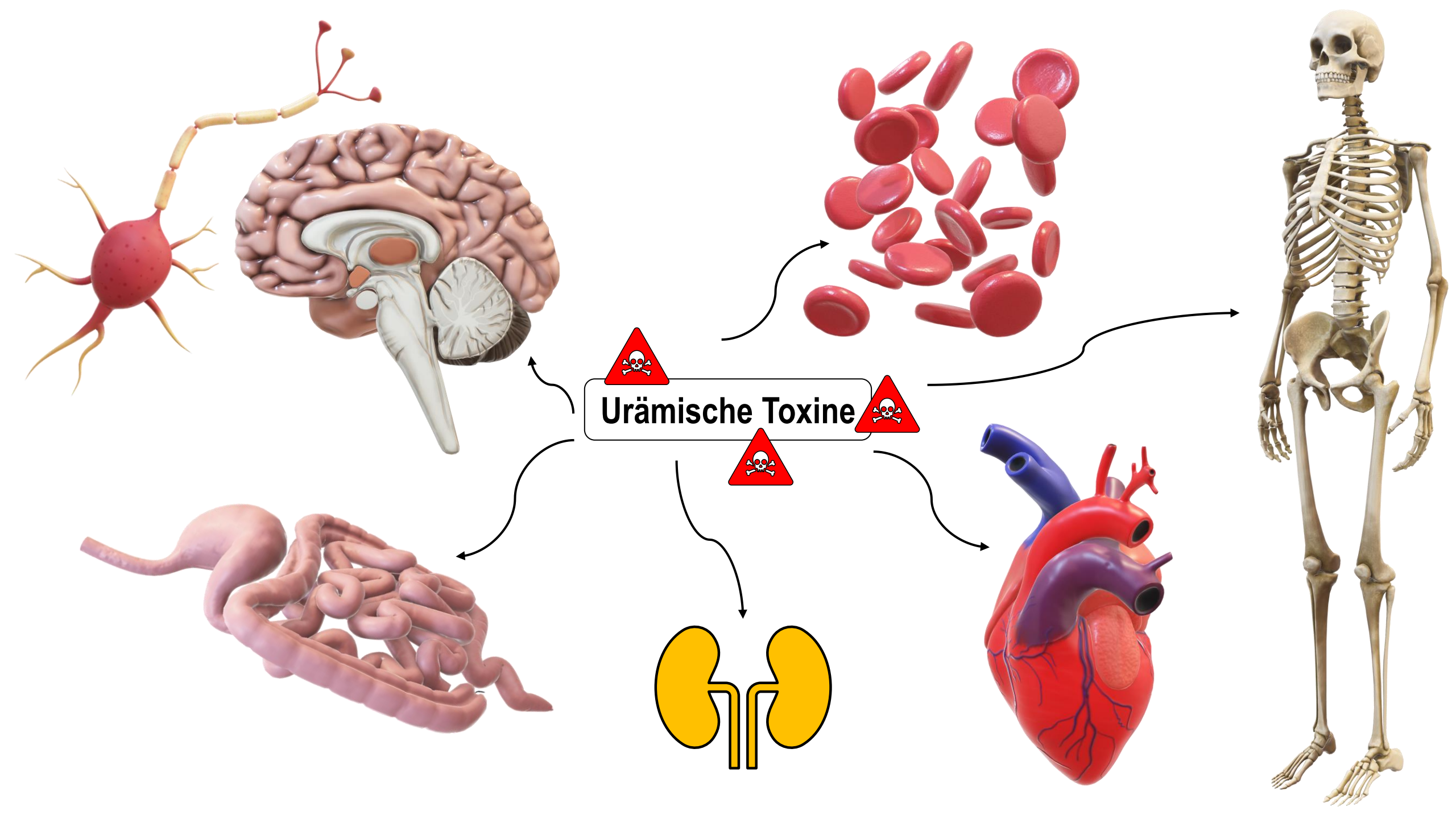
Entfernbar durch spezifische Dialyse-Membranen mit großen Poren

Beispiele: Leptin, β2-Mikroglobulin

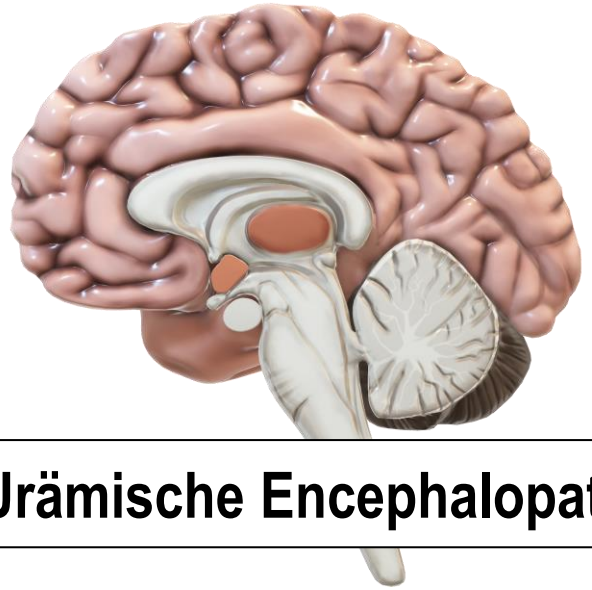
Falconi CA et al. Uremic Toxins: An Alarming Danger Concerning the Cardiovascular System. Front Phys. 2021;12.

Urämische Toxine – Feline Nierenerkrankung




Urämische Toxine

Urämie



Urämische Encephalopathie

Vet Pathol **42**:642–649 (2005)

Hypertensive Encephalopathy in Cats with Reduced Renal Function

C. A. Brown, J. S. Munday, S. Mathur, and S. A. Brown

J. Comp. Path. 2020, Vol. 180, 100–104

Available online at www.sciencedirect.com

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www.elsevier.com/locate/jcpa

SPONTANEOUSLY ARISING DISEASE

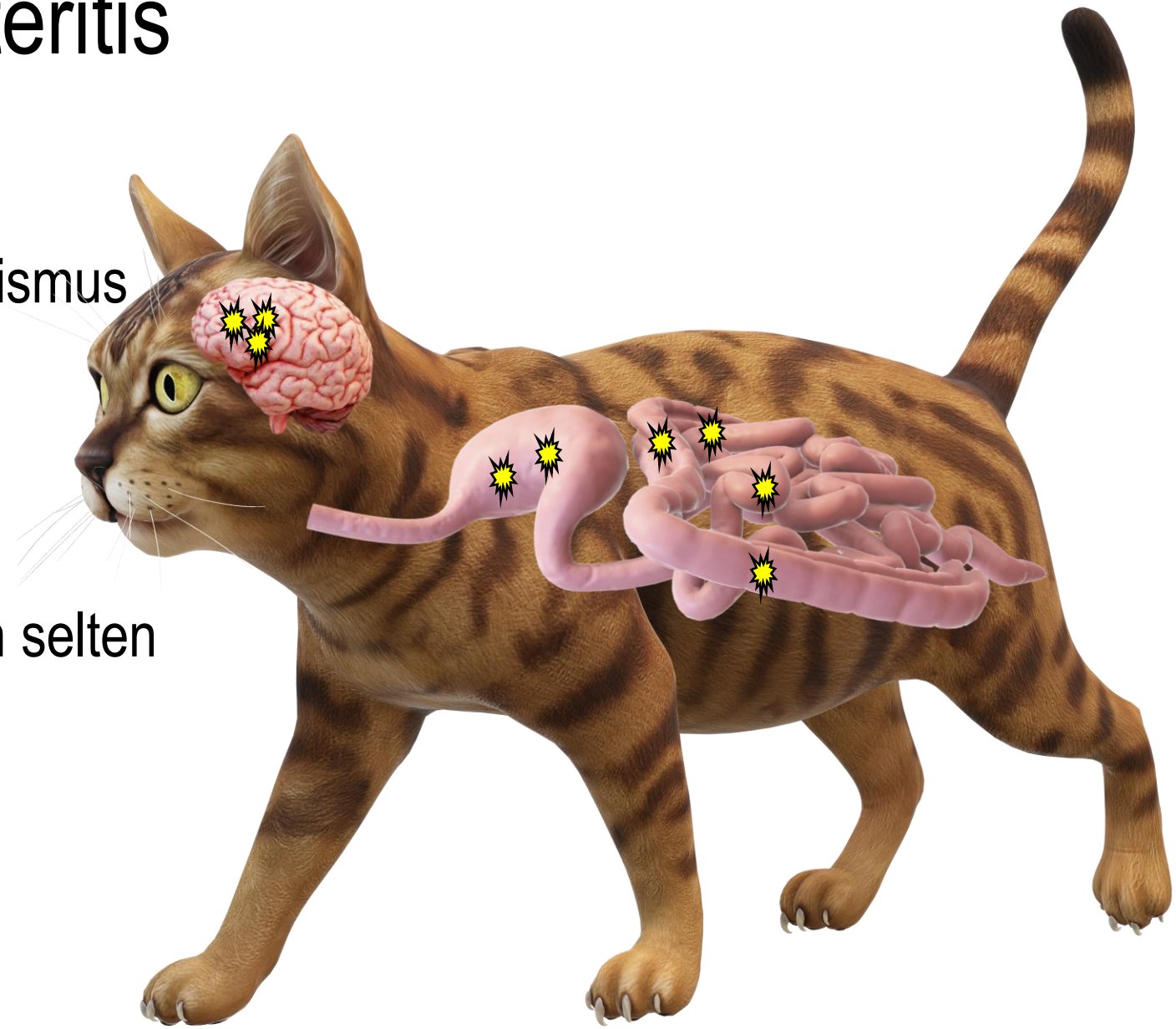
Uraemic Encephalopathy in a Persian Cat with Chronic Kidney Disease

Mizael Machado*, Tais M Wilson†, Davi E R Sousa†, Alexandra A B Gonçalves†, Christine S Martins‡ and Marcio B Castro†

Urämische Gastroenteritis

Anorexie

- Multifaktorieller Pathomechanismus
  - Urämische Toxine
  - „anorectic factor“



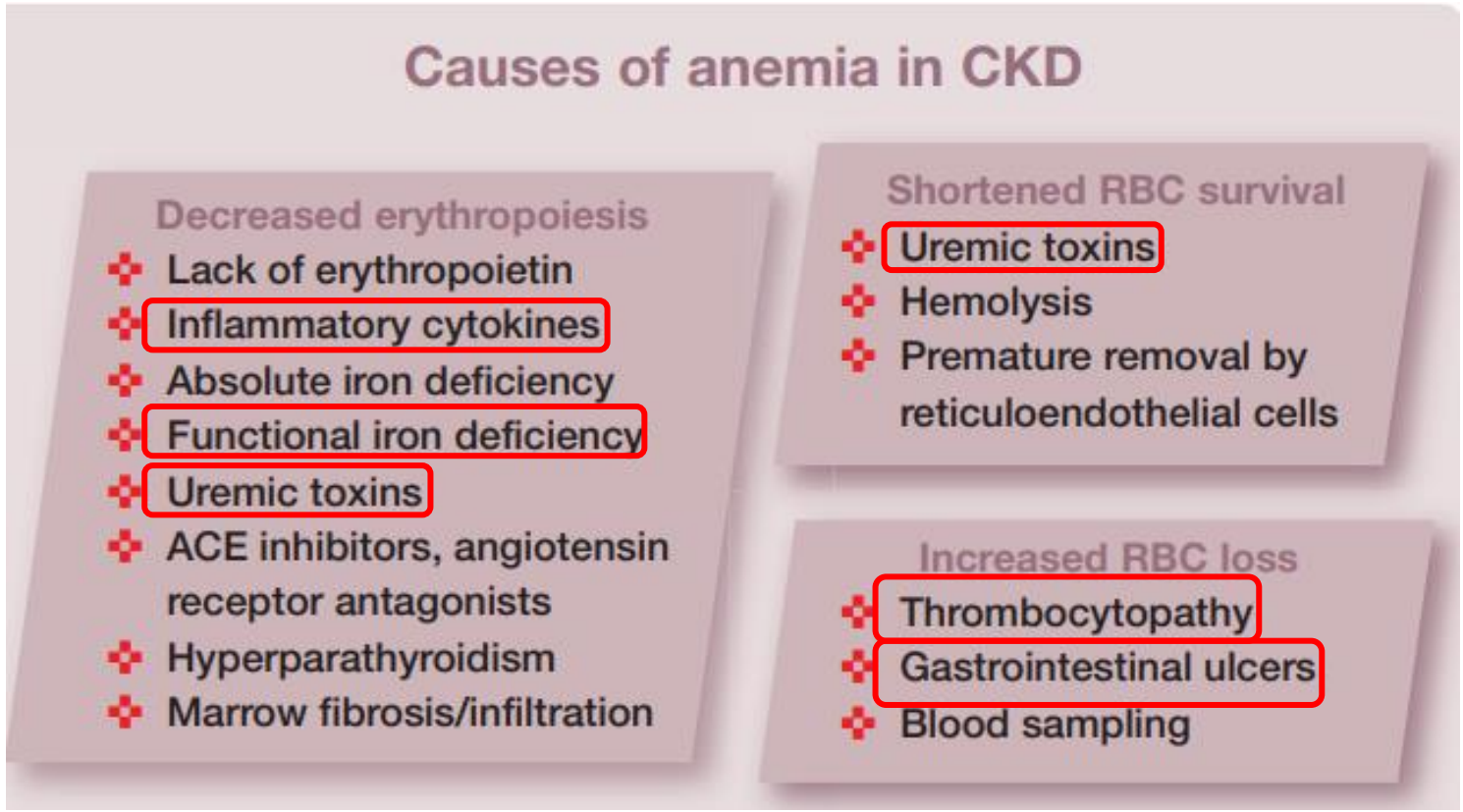
- Gastrointestinale Ulzerationen selten
- Gastrale Fibrosierung
- Gastrale Mineralisierung

Anämie im Rahmen der Nierenerkrankung

Journal of Feline Medicine and Surgery (2011) **13**, 629–640
doi:10.1016/j.jfms.2011.07.016

ANEMIA OF RENAL DISEASE
What it is, what to do and what's new

Serge Chalhoub, Cathy Langston and Adam Eatroff



Beeinflussung des Knochenstoffwechsels

Box 1
Consequences of chronic kidney disease–mineral and bone disorder in dogs and cats

Known to occur

- Renal secondary hyperparathyroidism
- Accelerated progression of kidney disease
- Increased mortality rate
- Renal osteodystrophy
- Cardiac arrhythmia
- Extraskeletal calcification
- Hypocalcemia
- Hypercalcemia
- Hypomagnesemia
- Hypermagnesemia

Likely to occur

- Decreased bone density
- Vessel calcification

Not recognized

- Pulmonary hypertension
- Atherosclerosis
- Valvular calcification
- Tertiary hyperparathyroidism
- Impaired skeletal response to PTH
- Adynamic bone disease

Update on Mineral and Bone Disorders in Chronic Kidney Disease

Vet Clin Small Anim ■ (2016)

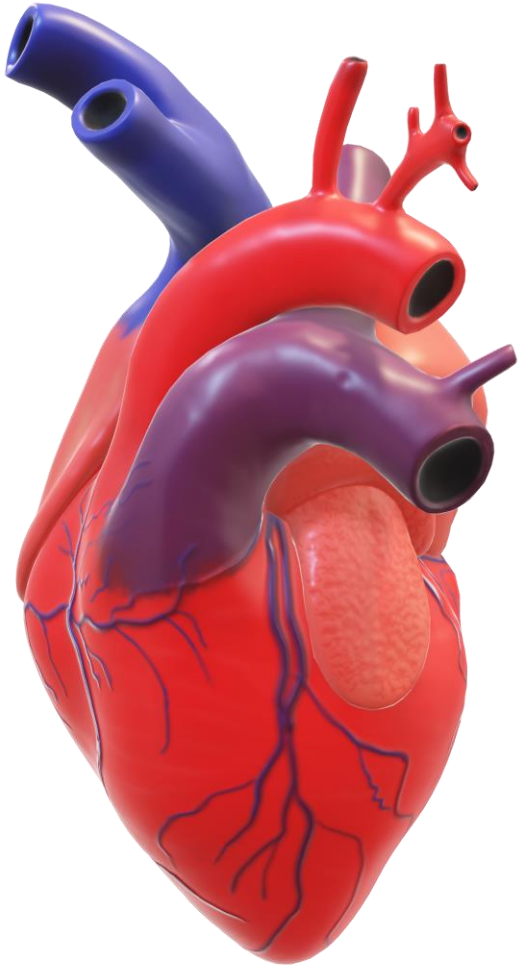
Jonathan D. Foster, VMD

Kardiorenale Achse

Cardiovascular–renal axis disorders in the domestic dog and cat: a veterinary consensus statement

J. L. Pouchelon*, C. E. Atkins†, C. Bussadori‡, M. A. Oyama§, S. L. Vaden†, J. D. Bonagura¶, V. Chetboul*, L. D. Cowgill||, J. Elliot**, T. Francey††, G. F. Grauer‡‡, V. Luis Fuentes§§, N. Sydney Moise¶¶, D. J. Polzin||||, A. M. Van Dongen*** and N. Van Israël†††

Journal of Small Animal Practice (2015) **56**, 537–552
DOI: 10.1111/jsap.12387



Urämische Toxine in der Veterinärmedizin

- Harnstoff
- Kreatinin
- Cystatin C
- Indoxylsulfat
- p-Cresylsulfat
- Parathormon
- SDMA

Nur wenige als Messwerte verfügbar
Auswirkungen der einzelnen urämischen Toxine oft unbekannt

Harnstoffkonzentration ↔ Konzentration zahlreicher urämischer Toxine

Urämische Toxine in der Veterinärmedizin

Harnstoff

Kreatinin

Cystatin C

Indoxylsulfat

p-Cresylsulfat

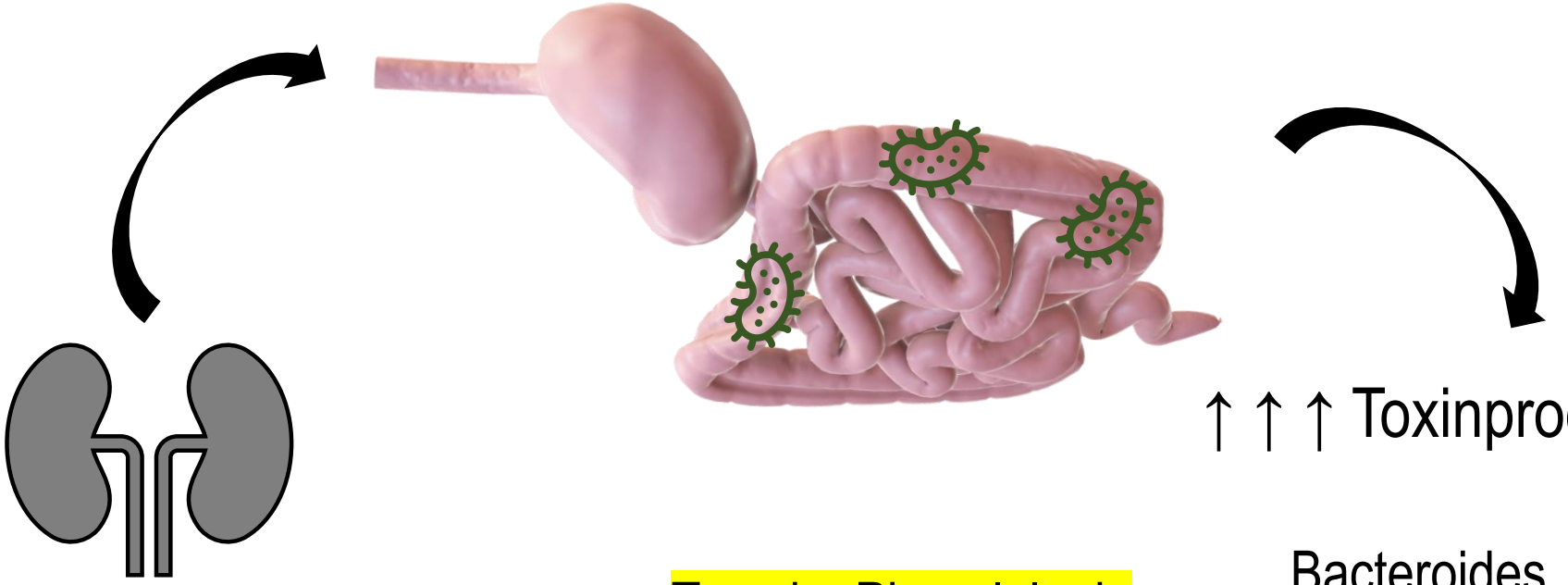
Parathormon

SDMA

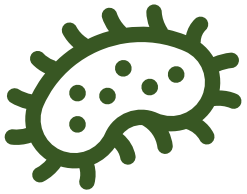
Neuwertige renale Biomarker

- Retinol binding protein
- B2-Mikroglobulin

Indoxylsulfat und p-Cresolsulfat



↑ ↑ ↑ Toxinproduzierende Bakterien

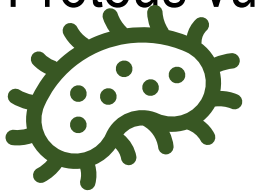


Tyrosin, Phenylalanin
⇒ p-Cresolsulfat

Bacteroides, Lactobacillus,
Enterobacter, Bifidobacterium,
Clostridium

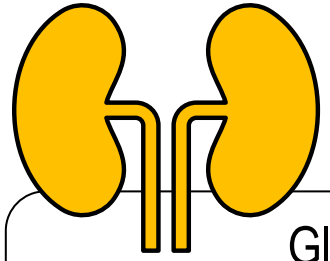
Tryptophan
⇒ Indoxylsulfat

Escherichia coli, Proteus vulgaris,
Bacteroides spp.



Auswirkungen spezifischer urämischer Toxine

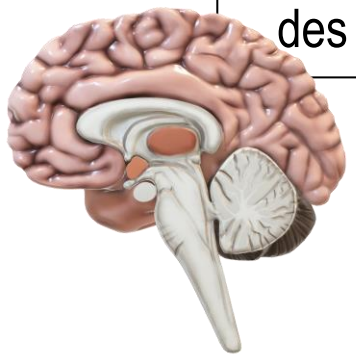
↑↑↑Indoxylsulfat, p-Cresylsulfat



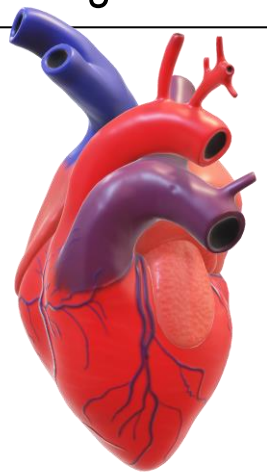
Glomeruläre Sklerose
Renale Fibrose
Entzündung und Schädigung der Tubuluszellen

↓EPO-Produktion

Störung der Funktion des Nervensystems



↑Risiko kardiovaskulärer Erkrankungen



Beeinflussung des Knochenstoffwechsels

Detection of indoxyl sulfate levels in dogs and cats suffering from naturally occurring kidney diseases

F.P. Cheng [a, 1], M.J. Hsieh [a ,b, 1], C.C. Chou [a], W.L. Hsu [c], Y.J. Lee [b, d, *]

Volume 205, Issue 3, September 2015, Pages 399-403

↑Indoxylsulfat bei Katzen mit Nierenerkrankung
Indoxylsulfat-Konzentration höher bei Azotämie

Plasma indoxyl sulfate concentration predicts progression of chronic kidney disease in dogs and cats

C.N. Chen[a,1], C.C Chou[b,1], P.S.J. Tsai[c,e], Y.J. Lee[a,d,*]

The Veterinary Journal 232 (2018) 33–39

Indoxylsulfat = Biomarker der Progression der Nierenerkrankung
Korrelation zwischen Indoxylsulfat und ↑Urea, Crea, P und ↓Hkt

DOI: 10.1111/jvim.15389

Journal of Veterinary Internal Medicine Open Access ACVIM American College of Veterinary Internal Medicine

STANDARD ARTICLE

The fecal microbiome and serum concentrations of indoxyl sulfate and p-cresol sulfate in cats with chronic kidney disease

Stacie C. Summers[1] | Jessica M. Quimby[1] | Anitha Isaiah[2] | Jan S. Suchodolski[2] | Paul J. Lunghofer[1] | Daniel L. Gustafson[1]

↓Vielfalt des fäkalen Mikrobioms
↑Indoxylsulfatkonzentration bei Katzen mit CNE
Konzentration urämischer Toxine bei Katzen mit CNE IRIS stage 2 ≈ IRIS stage 3 und 4
↑Indoxylsulfatkonzentration => ↓Appetit

DOI: 10.1111/jvim.15634

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access ACVIM American College of Veterinary Internal Medicine

Preliminary evaluation of fecal fatty acid concentrations in cats with chronic kidney disease and correlation with indoxyl sulfate and p-cresol sulfate

Stacie Summers[1] | Jessica M. Quimby[2] | Robert Kyle Phillips[3] | Jonathan Stockman[1] | Anitha Isaiah[3] | Jonathan A. Lidbury[3] | Joerg M. Steiner[3] | Jan Suchodolski[3]

↑Isovaleriansäure (fäkal) bei Katzen mit CNE
Korrelation zwischen der fäkalen Konzentration verzweigtkettiger Fettsäuren und pCresolsulfat
↑Konzentration verzweigtkettiger Fettsäuren bei ↓muscle score => Malassimilation

Therapieziel:

Reduktion der Konzentration urämischer Toxine

⇒↓Risiko einer urämischen Krise

⇒Verlangsamung der Progression der Nierenerkrankung

⇒Erhalt der Lebensqualität und Verbesserung der Überlebenszeit

Urämische Toxine - Klassifikation

Wasserlösliche Moleküle

<500 Da

Leicht entfernbar durch Hämodialyse

Beispiele: Harnstoff, Kreatinin

Proteingebundene Moleküle

Nur ungebundene Fraktion durch Dialyse entfernbar

Beispiele: Indole, Phenole

Moleküle mittlerer Größe

>500 Da

Entfernbar durch spezifische Dialyse-Membranen mit großen Poren

Beispiele: Leptin, β2-Mikroglobulin

Falconi CA et al. Uremic Toxins: An Alarming Danger Concerning the Cardiovascular System. Front Phys. 2021;12.

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Beispiele: Leptin, β2-Mikroglobulin

Veterinärmedizinische Fakultät Klinik für Kleintiere, Innere Medizin, Justus-Liebig-Universität Gießen

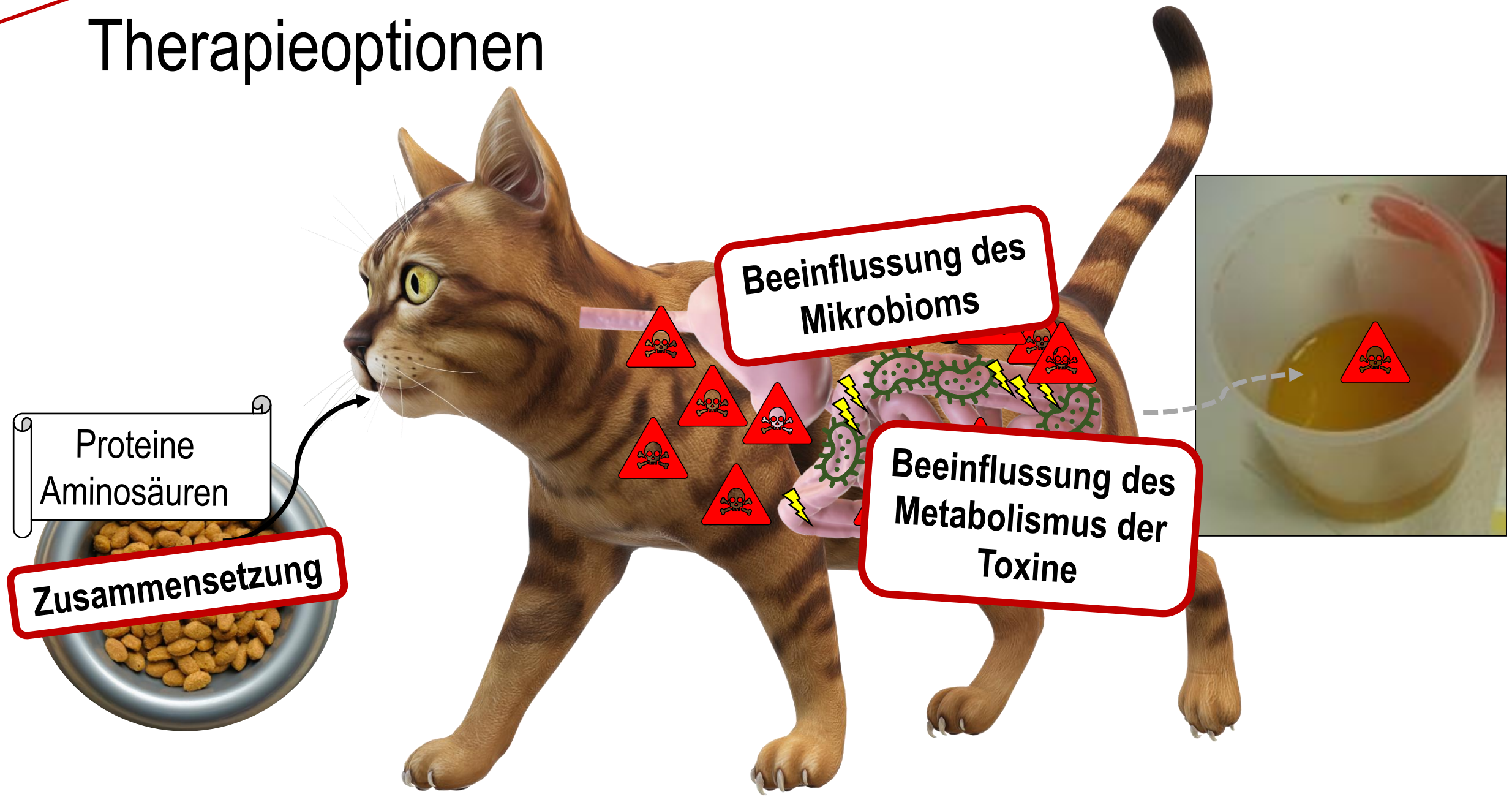
Falconi CA et al. Uremic Toxins: An Alarming Danger Concerning the Cardiovascular System. Front Phys. 2021;12.

Veterinärmedizinische Fakultät Klinik für Kleintiere,
Innere Medizin, Justus-Liebig-Universität Gießen

Dialyseverfahren

- Keine Bedeutung bei CNE
- Kosten
- Dauerhafte Therapie
- Unethisch
- Geringe Verfügbarkeit
- Nebenwirkungen/Folgeerscheinungen

Therapieoptionen



Ephraim E, et al., J Food Sci Nutr 2021, 7: 096
DOI: 10.24966/FSN-1076/100096

HSOA Journal of Food Science and Nutrition

Research Article

High Protein Consumption with Controlled Phosphorus Level Increases Plasma Concentrations of Uremic Toxins in Cats with Early Chronic Kidney Disease

Eden Ephraim[1]* and Dennis E Jewell[2]

↑Proteine => ↑urämische Toxine

Modifikation der Futterzusammensetzung

Nierendiät

- ↓P, ↓Na
- ↑Omega-3 polyungesättigte Fettsäuren und Antioxidantien
- ↓Protein

Journal of the American Veterinary Medical Association
September 15, 2006, Vol. 229, No. 6, Pages 949-957
https://doi.org/10.2460/javma.229.6.949

Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats

Sheri J. Ross, DVM, PhD, DACVIM; Carl A. Osborne, DVM, PhD, DACVIM; Claudia A. Kirk, DVM, PhD, DACVN, DACVIM; Stephen R. Lowry, PhD; Lori A. Koehler; David J. Polzin, DVM, PhD, DACVIM

↓Urämische Episoden

↓Mortalitätsrate

Modifikation der Futterzusammensetzung

IRIS International Renal Interest Society

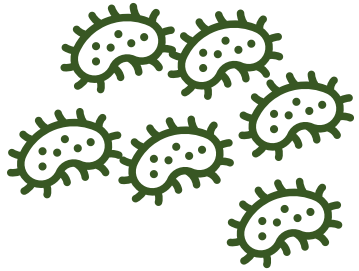
Treatment Recommendations for CKD in Cats (2023)

Stage 2 Feline patients:

All of the above listed for Stage 1 (listed here again for convenience) plus any additional steps indicated.

1. Discontinue all potentially nephrotoxic drugs if possible.
2. Identify and treat any pre-renal or post-renal abnormalities.
3. Rule out any treatable conditions like pyelonephritis and ureteral obstruction with radiographs and/or ultrasonography.
4. Measure blood pressure and urine protein to creatinine ratio (UP/C).
5. Consider feeding a clinical renal diet: this may be accomplished more easily early in the course of CKD, before inappetence develops.

Beeinflussung des Mikrobioms



Einfluss von Pro-/Präbiotika => Erhalt der intestinalen Flora

Azodyl, a synbiotic, fails to alter azotemia in cats with chronic kidney disease when sprinkled onto food

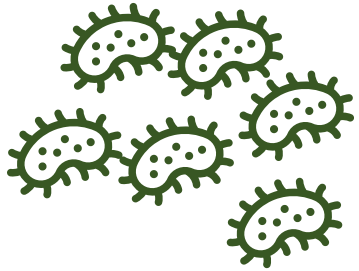
Mark Rishniw BVSc, MS, PhD, DACVIM[1*], **Susan G Wynn** DVM[2]

Journal of Feline Medicine and Surgery (2011) **13**, 405–409
doi:10.1016/j.jfms.2010.12.015

Kein Effekt auf Azotämie
Beeinflussung durch Applikationsform?

medpets

Beeinflussung des Mikrobioms



Einfluss von Pro-/Präbiotika => Erhalt der intestinalen Flora

PLOS ONE

PLOS ONE | https://doi.org/10.1371/journal.pone.0268624 May 24, 2022

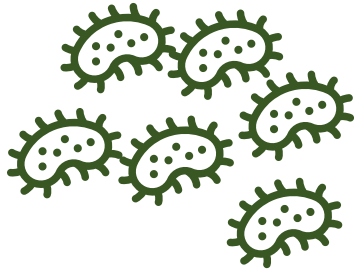
RESEARCH ARTICLE

Feeding cats with chronic kidney disease food supplemented with betaine and prebiotics increases total body mass and reduces uremic toxins

Jean A. Hall[1]*, Dennis E. Jewell[2], Eden Ephraim[3]

1 Department of Biomedical Sciences, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon, United States of America, **2** Department of Grain Science and Industry, Kansas State University, Manhattan, Kansas, United States of America, **3** Pet Nutrition Center, Hill's Pet Nutrition, Topeka, Kansas, United States of America

Beeinflussung des Mikrobioms



Einfluss von Pro-/Präbiotika => Erhalt der intestinalen Flora

Beeinflussung des Metabolismus

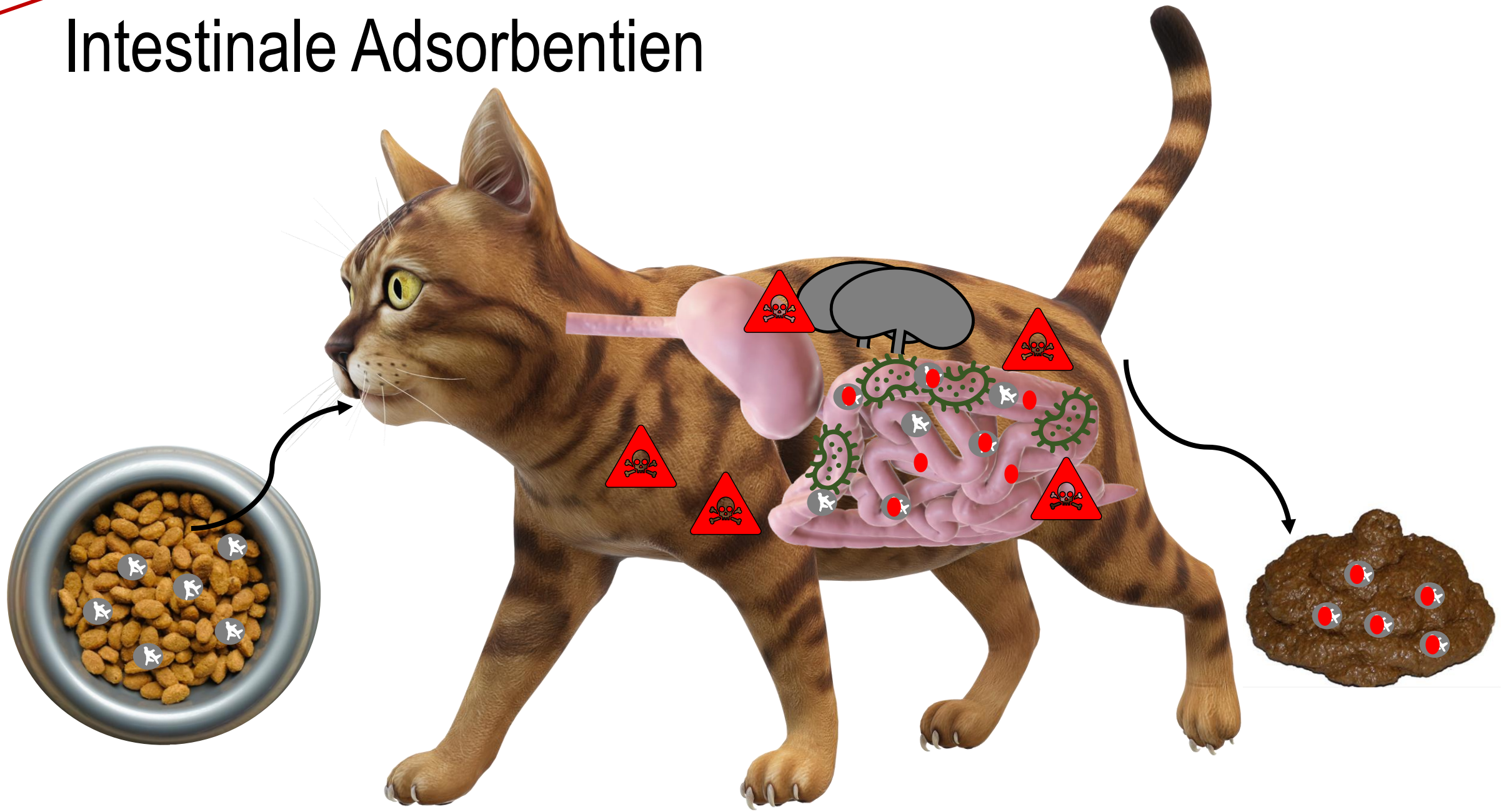
Intestinale Adsorbentien

⇒Bindung der Vorstufen urämischer Toxine

⇒Reduktion der Konzentration urämischer Toxine

Renaltec

Intestinale Adsorbentien



Intestinale Adsorbentien

Renaltec

⇒Bindung von Indol

⇒↓Indoxylsulfat

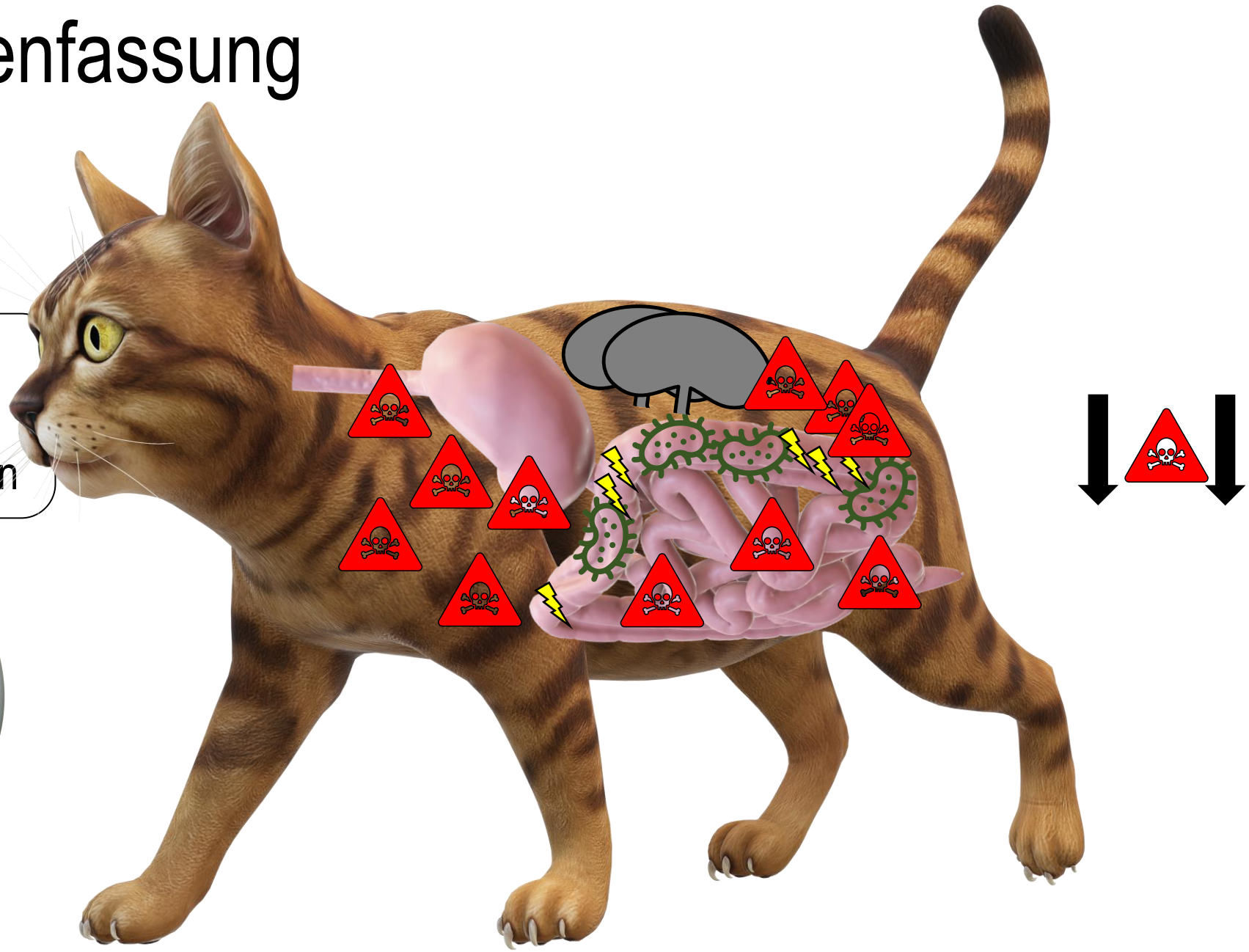
Renaltec attenuates serum levels of indoxyl sulfate in geriatric cats

Jose Mottet[1], Nikolaus Kowollik[2]

BSAVA congress 2019 proceedings.

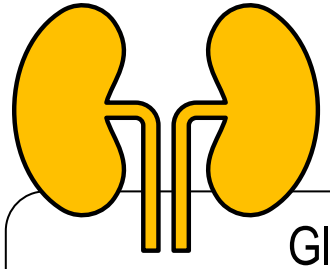
Zusammenfassung

Nierendiät
Prä-/Probiotika
Intestinale Adsorbentien



Auswirkungen spezifischer urämischer Toxine

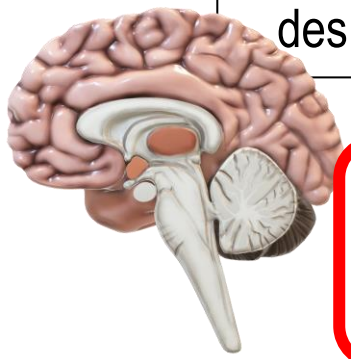
↑↑↑Indoxylsulfat, p-Cresolsulfat



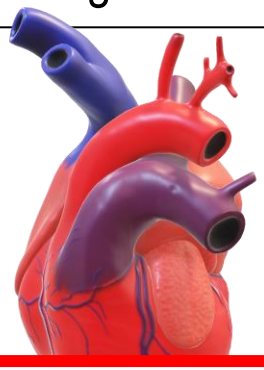
Glomeruläre Sklerose
Renale Fibrose
Entzündung und Schädigung der Tubuluszellen

↓EPO-Produktion

Störung der Funktion des Nervensystems



↑Risiko kardiovaskulärer Erkrankungen



Beeinflussung des Knochenstoffwechsels

⇒Verbesserung der Prognose nierenkranker Katzen
⇒Reduktion der Morbidität und Mortalität


FRAGEN?