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Are DON Congeners a Food Safety Concern?

James J. Pestka
Dept. of Food Science & Human Nutrition
Institute for Integrative Toxicology
Michigan State University
East Lansing, Michigan
pestka@msu.edu

Bottom Line

Using existing DON avoidance measures already in place in the U.S., evidence to date suggests that known congeners of this mycotoxin are not a food safety concern.

Acknowledgements

USWBI

USDA NIFA

NIH National Institute of Environmental Health Sciences
Your Environment. Your Health.

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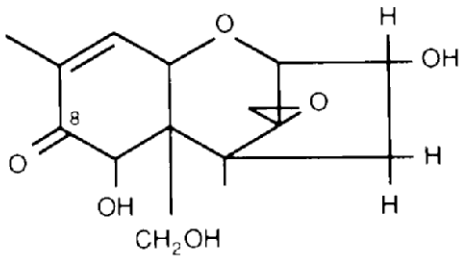
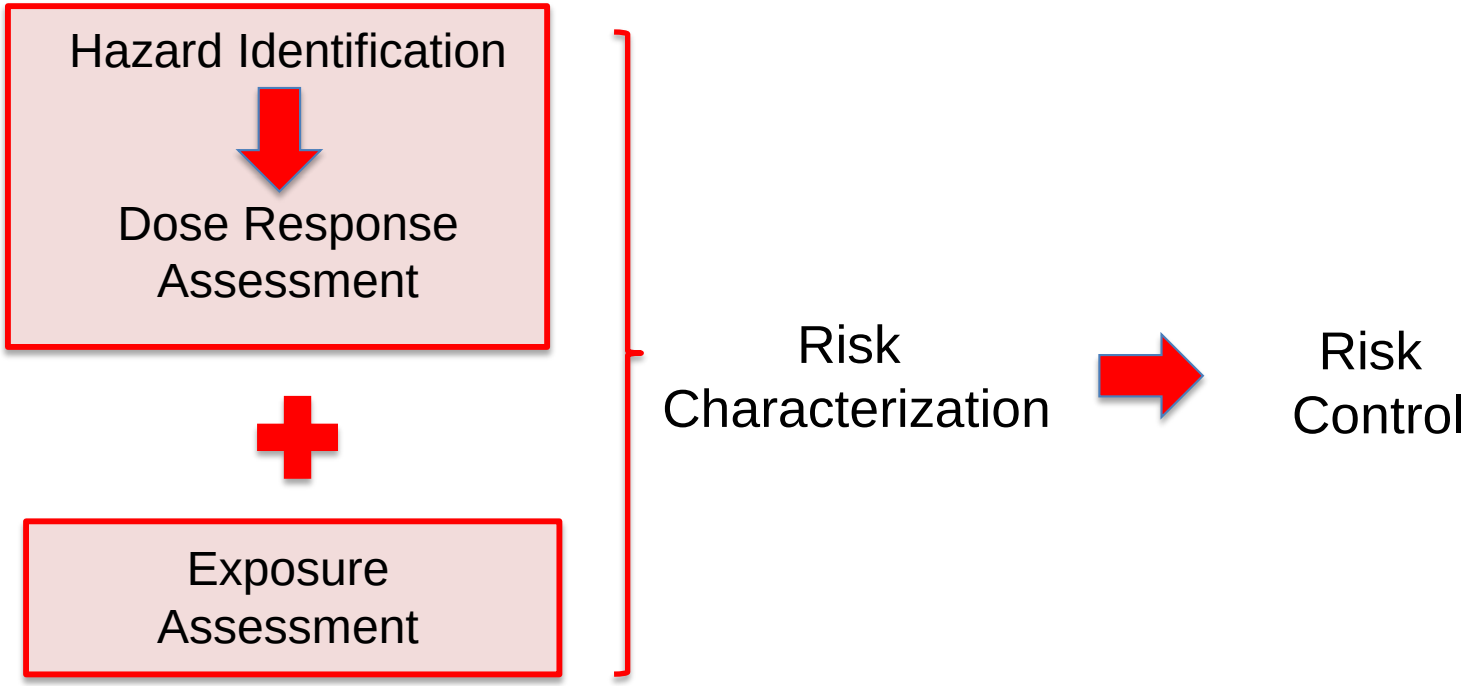
Deoxynivalenol (DON)



- "Vomitoxin," most common trichothecene associated with *Fusarium graminearum*
- Contaminates wheat, barley and corn
- Produced pre- and post-harvest
- Resistant to processing and baking
- Associated with human and animal illnesses

Safety Assessment Paradigm



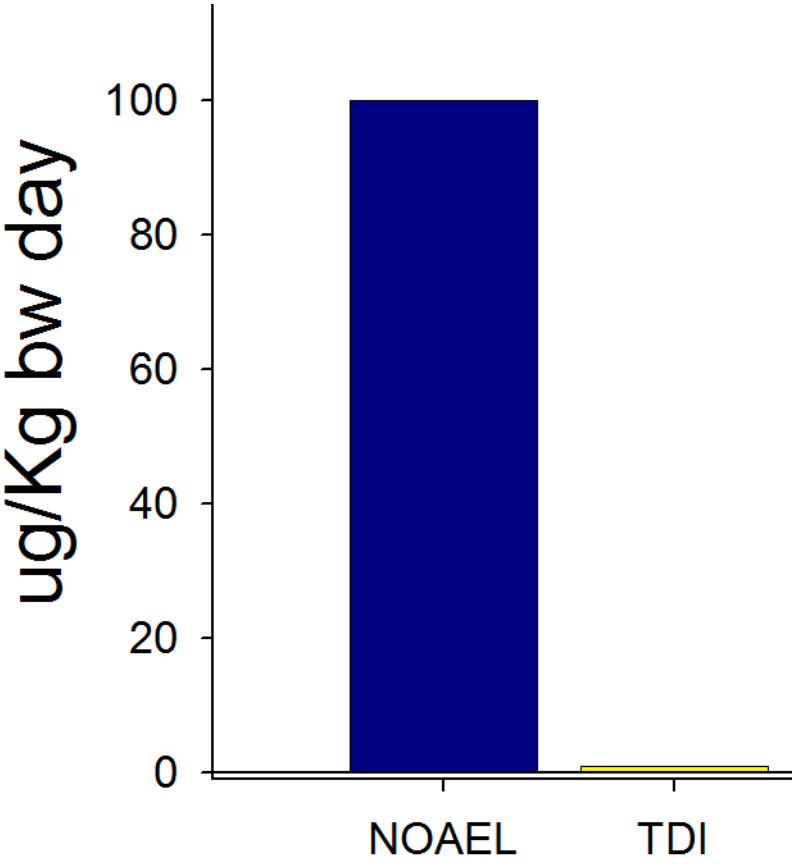
Toxicity x Exposure = Risk

Tolerable Daily Intake of DON is Based on Growth Suppression in Mice

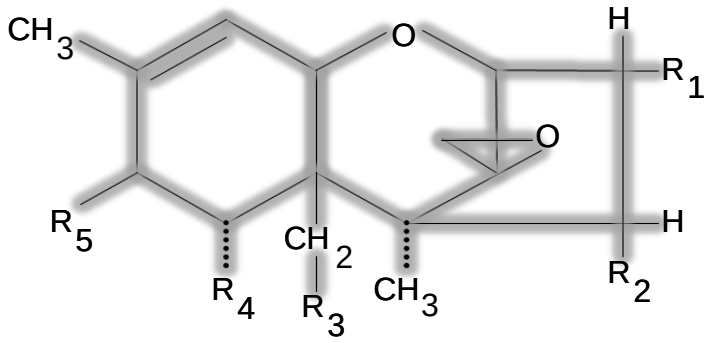
FDA	EFSA
Guidance Limit	Maximum Level
1000 µg/ kg grain Processed *Products*	200 - 1250 µg/ kg Processed to Unprocessed Grain Products
No Published Risk Assessment	Based on Iverson et. al (1995) and JECFA TDI

Canady et. al. 2001. JECFA47 Report.
FDA. 2010. http://www.fda.gov/downloads/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/NaturalToxins/UCM217558.pdf

DON Tolerable Daily Intake = NOAEL / 100-fold safety factor



Why should we worry about DON "congeners"?



- Can be produced as:
  - *Fusarium* co-metabolites with DON
  - Plant metabolites of DON
- Co-present with DON in wheat and barley
- Potential for similar toxic effects

Compound	R1	R2	R3	R4	R5
DON	OH	H	OH	OH	=O
3-ADON	OAc	H	OH	OH	=O
15-ADON	OH	H	OAc	OH	=O
NIV	OH	OH	OH	OH	=O
FX	OH	OAc	OH	OH	=O
DON-3 glucoside	OH	H	Glucose	OH	=O

Risk = Toxicity x Exposure

Assumption: Toxic effects of DON and its congeners are additive, therefore..

Risk of eating *Fusarium*-contaminated food $=$ $\sum ([DON] \times toxicity_{DON}) + ([DC_1] \times toxicity_{DC1}) + ([DC_2] \times toxicity_{DC2}) + \ldots\ldots + ([DC_n] \times toxicity_{DCn})$

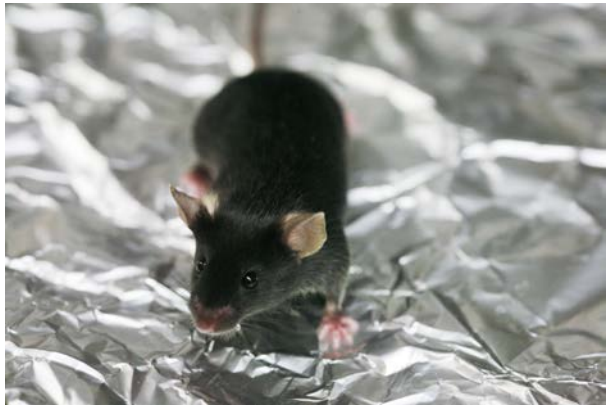
DC = DON Congener

Risk = Toxicity x Exposure

What are the relative toxic potencies of DON congeners in animal models for toxicity?

Models used to assess DON toxicity

Mink



Mouse

Nausea
Vomiting

Anorexia
Decreased weight gain

Cytokine storm
Immune dysregulation

Comparison of DON congener effects in mink emesis model

Congener	ED_{50} [a] (mg/kg bw)	Relative Potency[b]
DON	0.03	100
15-ADON	0.04	75
3-ADON	0.20	15
NIV	0.18	17
FX	0.03	100
D3G	>2.0	<2

[a]ED_{50} = Dose causing emesis in 50% of the animals tested. ED_{50} values were determined using a EPA Proc Probit model.

[b]Relative potency = ED_{50} DON/ ED_{50} DC x 100

Comparison of DON congener effects in mouse food refusal model

Congener	BMD[a] (mg/kg bw)	Relative Potency[b]
DON	1.5	100
3-ADON	1.3	100
15-ADON	1.2	100
NIV	0.5	300
FX	0.2	900
D3G	≈3.0	≈50

[a] Benchmark dose = dose that causes ≥10% decrease in food intake

[b] Relative potency = DON BMD /DC BMD x 100

Comparison of DON congener effects in mouse immunotoxicity model

Congener	Cytokine mRNA expression				
	IL-1β	IL-6	CXCL-2	CCL-2	CCL7
	Relative Potency[a]				
DON	100	100	100	100	100
3-ADON	38	19	18	35	40
15 -ADON	62	47	54	68	73
NIV	54	1	2	3	6
FX	200	1	40	87	60
D3G	15	1	0.2	0.3	6

[a] Relative potency = Fold change DON /Fold change DC x 100

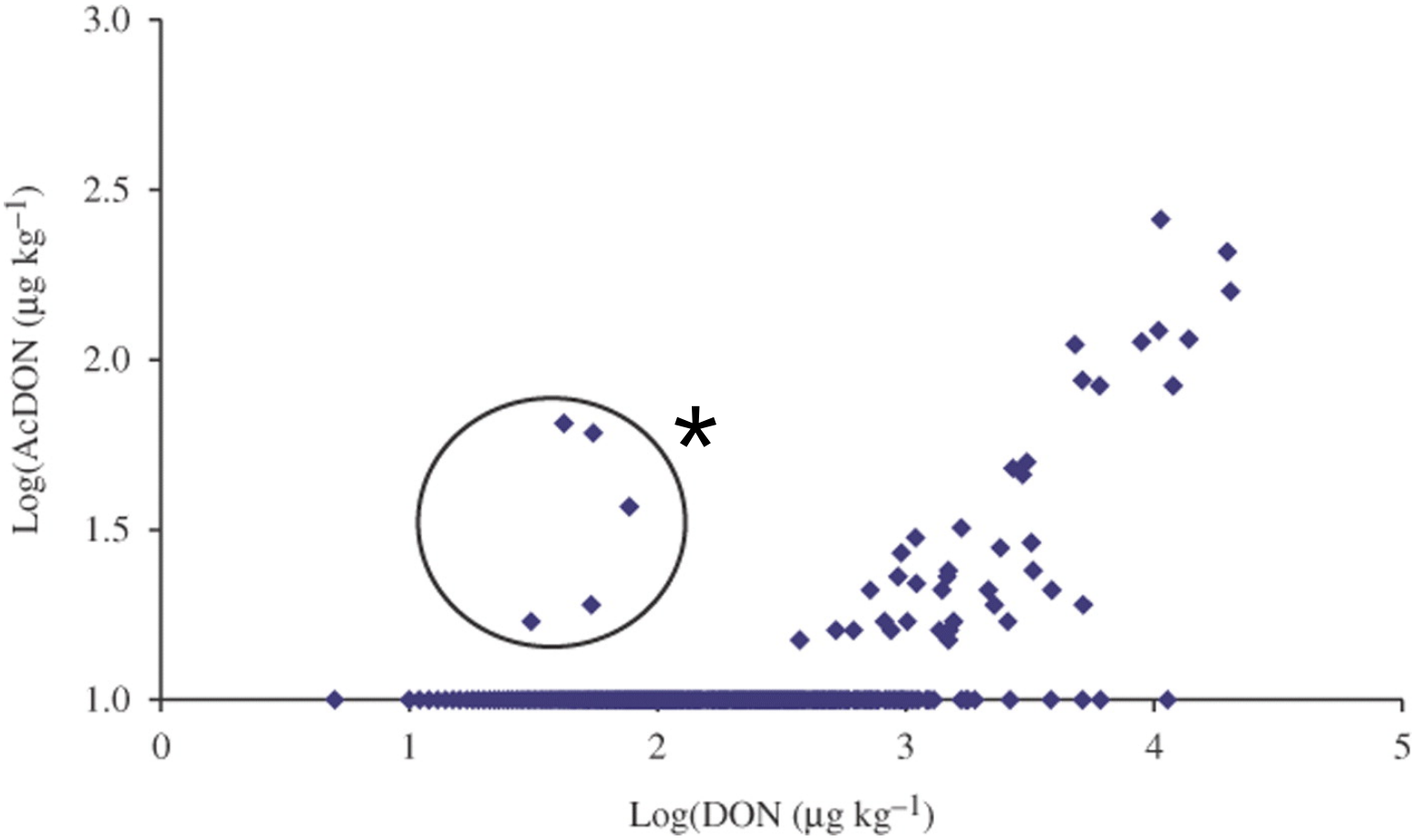
Summary of relative DON congener toxicities in the three animal models

Congener	Emesis	Anorexia	Immune
DON	100	100	100
3-ADON	80	100	30
15 -ADON	20	100	60
NIV	100	300	13
FX	20	900	78
D3G	2	≈50	5

Risk = Toxicity x Exposure

What is our exposure to DON congeners relative to DON?

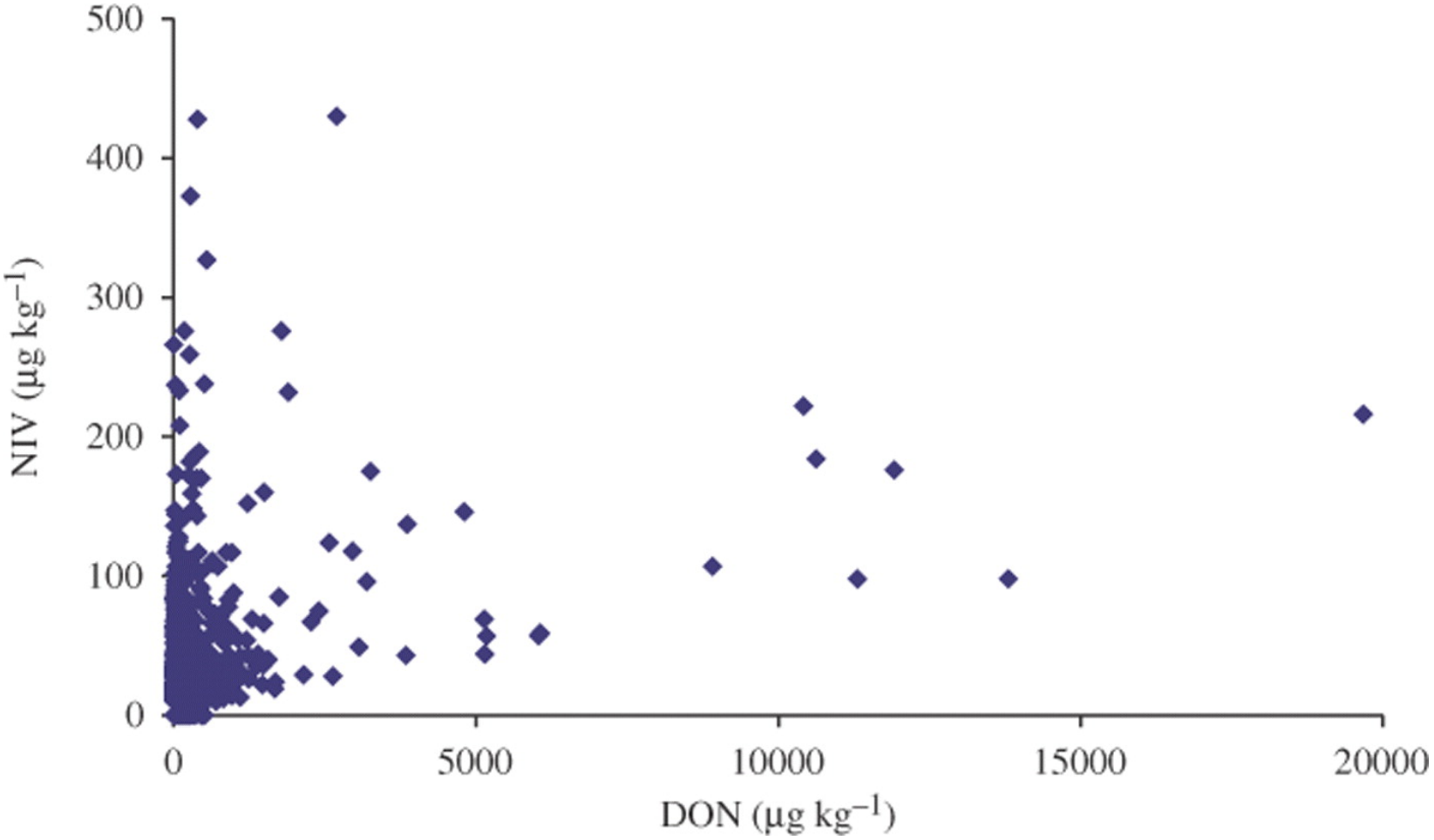
Relationship between AcDON (3- and 15-acetyl DON) and DON concentration for UK wheat, 2001–2005 (*n* = 1624).



* Samples with a high ratio of acetylated DON-to-DON are circled.

Published in: S.G. Edwards; *Food Additives & Contaminants: Part A* **2009,** 26, 496-506.
DOI: 10.1080/02652030802530679

Relationship between NIV and DON concentration for UK wheat, 2001–2005 (*n* = 1624).

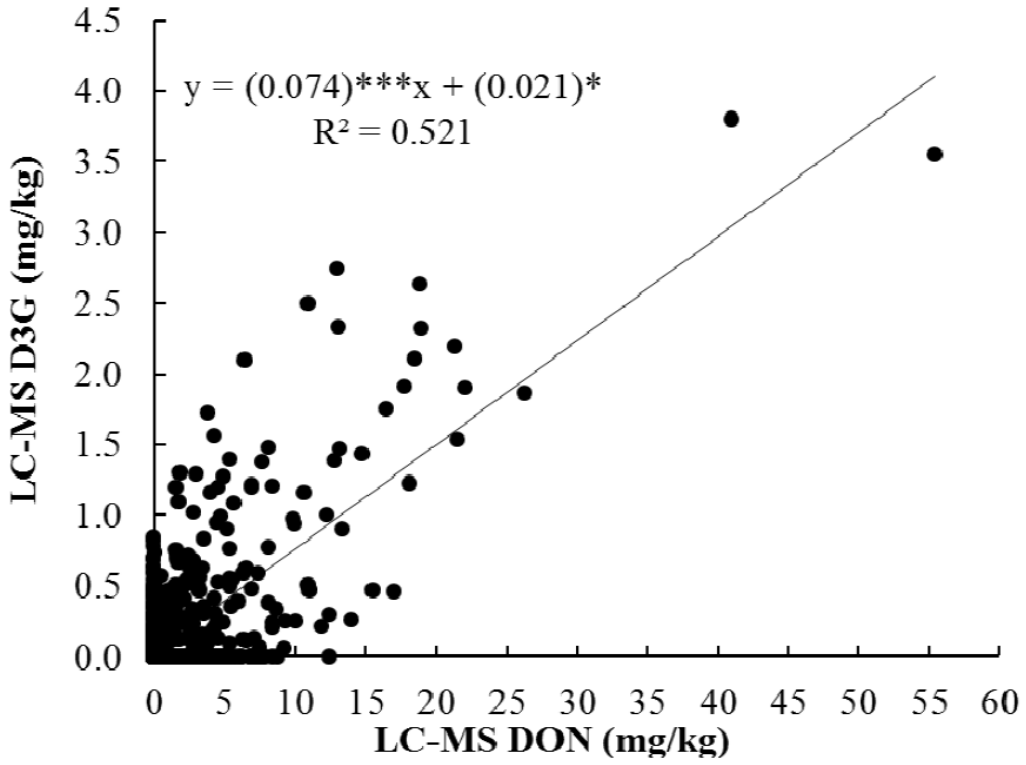


Published in: S.G. Edwards; *Food Additives & Contaminants: Part A* **2009,** 26, 496-506.
DOI: 10.1080/02652030802530679

Toxins **2013**, *5*, 2656-2670; doi:10.3390/toxins5122656

Occurrence of Deoxynivalenol and Deoxynivalenol-3-glucoside in Hard Red Spring Wheat Grown in the USA

Figure 3. Correlation between DON and D3G levels in survey samples between 2011 and 2012; where ***, and * indicate that regression coefficients are significant at $p < 0.001$ and $p < 0.05$, respectively.



Conclusions:

- Toxicity of DON congeners is generally ≤ DON
- Exposure to DON congeners is <<< DON

Risk of eating Fusarium-contaminated food = $\sum$ ([DON] x $toxicity_{DON}$) + ([DC_1] x $toxicity_{DC1}$) + ([DC_2] x $toxicity_{DC2}$) + ……+ ([DC_n] x $toxicity_{DCn}$)

Bottom Line

Using existing DON avoidance measures already in place in the U.S., evidence to date suggests that known congeners of this mycotoxin are not a food safety concern.

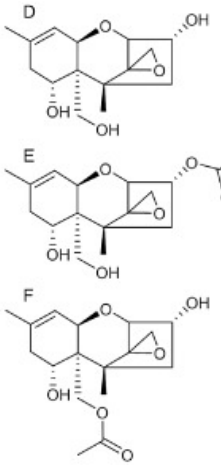
But……

New DON congeners have been/ are being identified

Toxins **2015**, *7*, 3112-3126; doi:10.3390/toxins7083112

The Metabolic Fate of Deoxynivalenol and Its Acetylated Derivatives in a Wheat Suspension Culture: Identification and Detection of DON-15-*O*-Glucoside, 15-Acetyl-DON-3-*O*-Glucoside and 15-Acetyl-DON-3-Sulfate

Environ Microbiol. 2015 Aug; 17(8): 2588–2600.

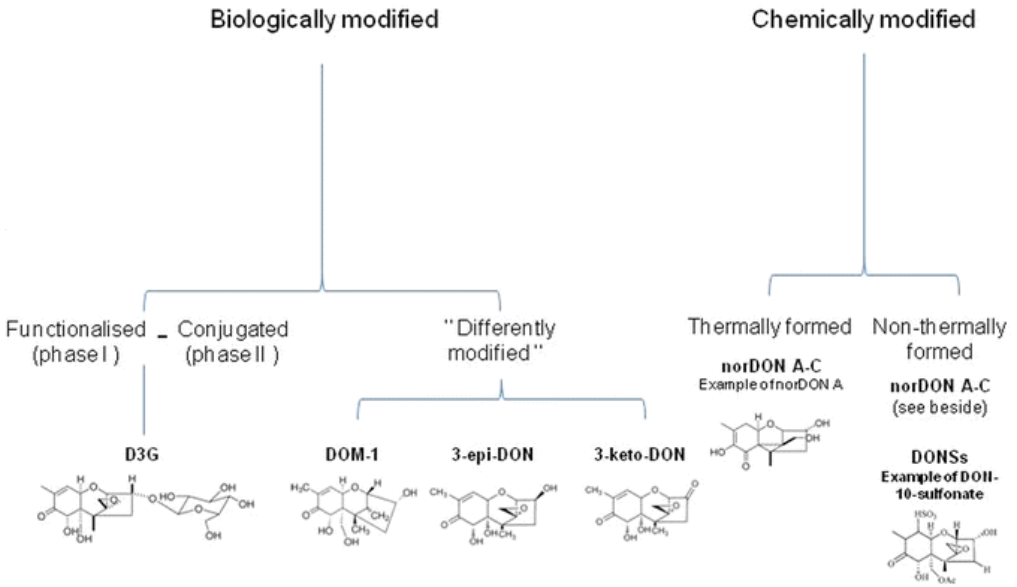


NX-3

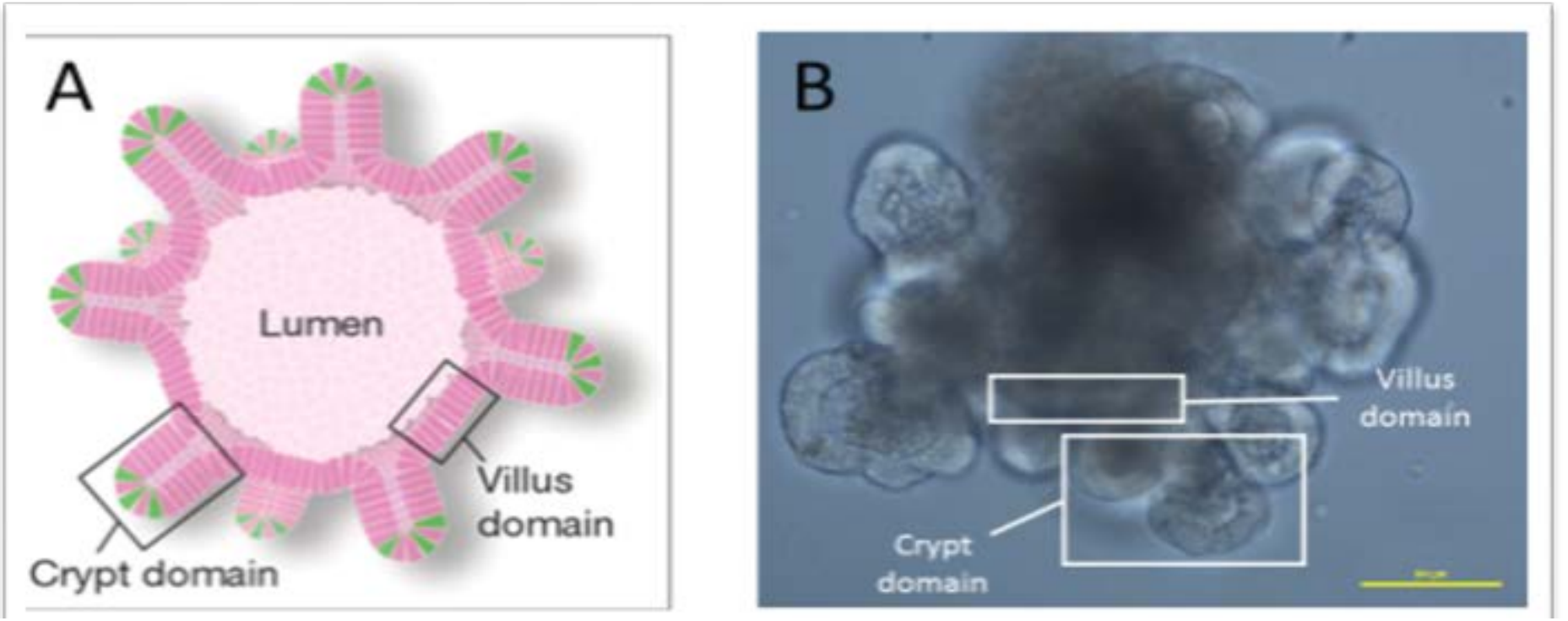
NX-2

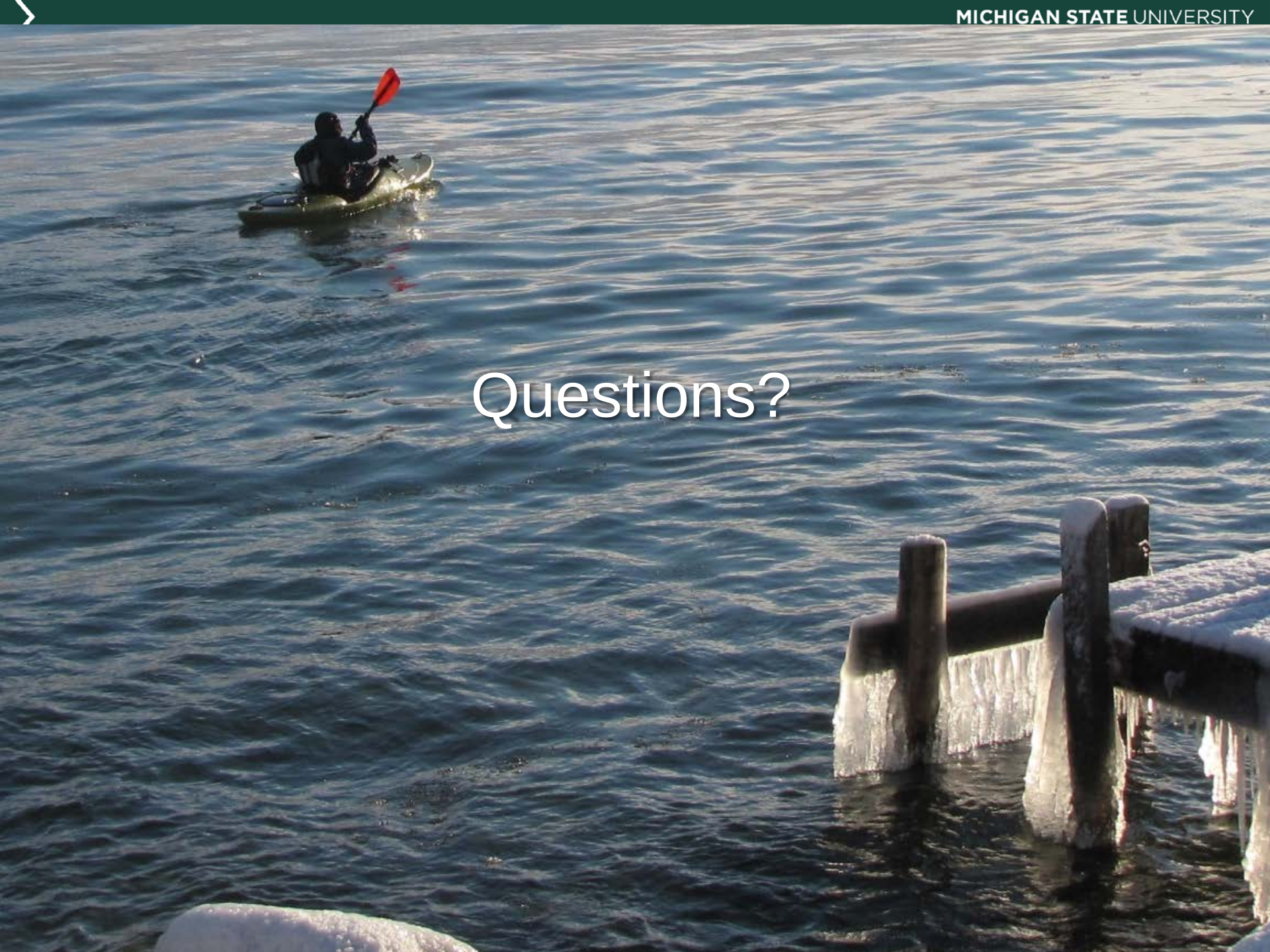
NX-4

Arch Toxicol (2016) 90:2931–2957
DOI 10.1007/s00204-016-1826-4



Ongoing Scab Project: Develop mini-gut organoid cultures to predict DON congener toxicity




Questions?