



UiO : Faculty of Medicine  
University of Oslo

# CHALLENGES OF SETTING NUTRIENT REFERENCE VALUES AND CUT-OFFS FOR DEFINING DEFICIENCIES AND EXCESS IN PEDIATRIC POPULATIONS

TRIAL LECTURE

ULF WIKE LJUNGBLAD



AN APPLE A DAY KEEPS THE DOCTOR AWAY



DIETARY REFERENCE VALUES  
REFERENCE INTERVALS



# DISPOSITION 45 MINUTES



ORGANIZATIONS



DEFINITIONS



DIETARY REFERENCE VALUES



CUT-OFFS FOR DEFINING DEFICIENCIES  
AND EXCESS



PUTTING IT TOGETHER WITH SELENIUM



CONCLUSIONS

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CONCLUSIONS



RESEARCH

IMPLEMENTATION

POLICY

RECOMMENDATION

WORLD HEALTH ORGANIZATION

NATIONAL ACADEMIES OF  
SCIENCE, ENGINEERING,  
AND MEDICINE (USA)  
NASEM

EUROPEAN FOOD SAFETY  
AUTHORITY  
EFSA

NORDIC  
COUNCIL

HARMONIZATION

NORDIC NUTRITION  
RECOMMENDATION  
S  
NNR2023

ALLEN ET AL.  
2020

# NORDIC NUTRITION RECOMMENDATIONS 2023 NNR2023 (6TH EDITION)

- NNR2023 REPORT
- SYSTEMATIC REVIEWS
- BACKGROUND REVIEWS
- INTERNATIONAL HARMONIZATION



# INDUSTRY FINANCED RESEARCH

A FAVORABLE CONCLUSION IS MORE LIKELY  
“INDUSTRY BIAS”

HANSEN ET AL. 2019

LUNDH ET AL. 2017



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DIETARY REFERENCE VALUES



CUT-OFFS FOR DEFINING DEFICIENCIES AND EXCESS



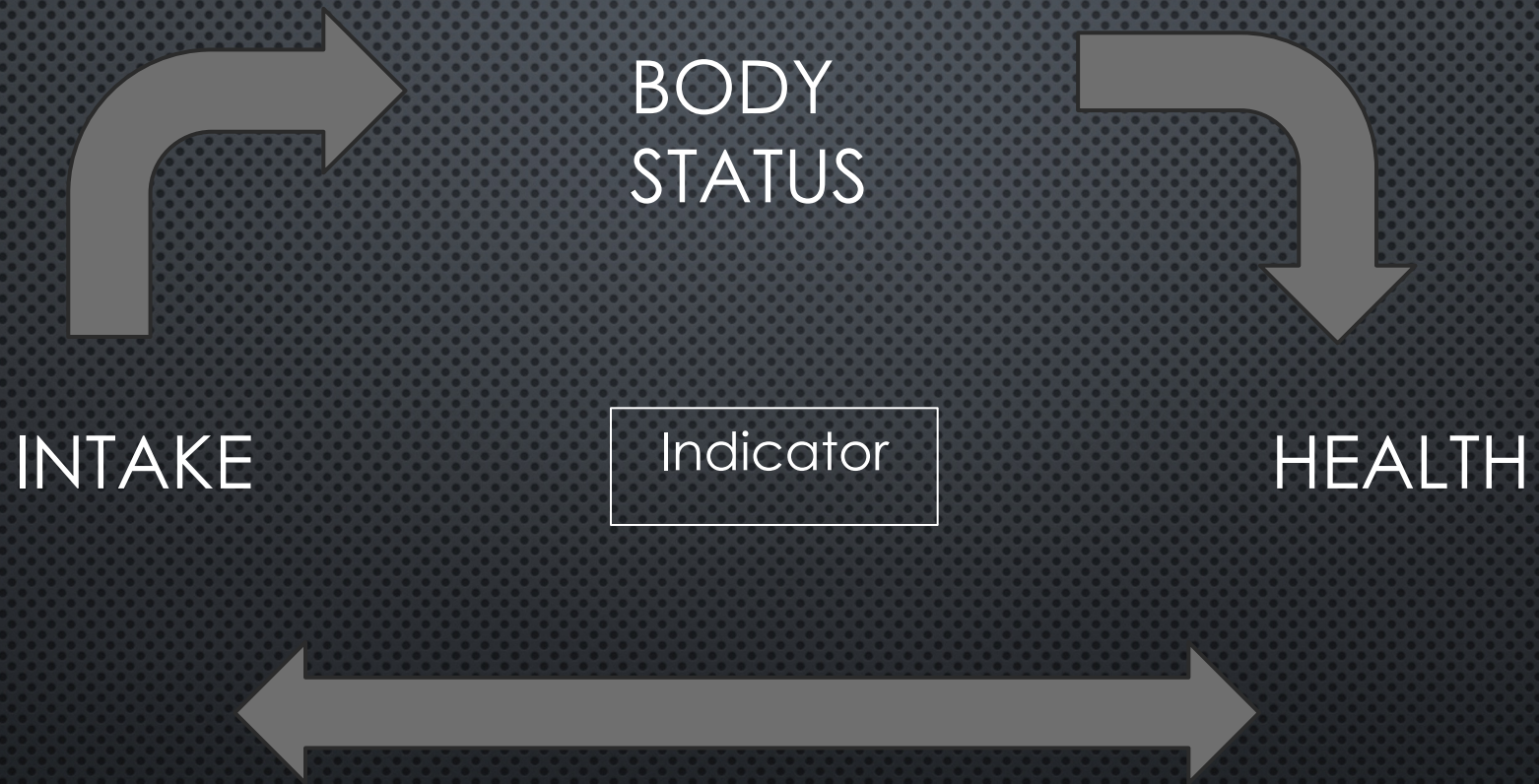
PUTTING IT TOGETHER WITH SELENIUM

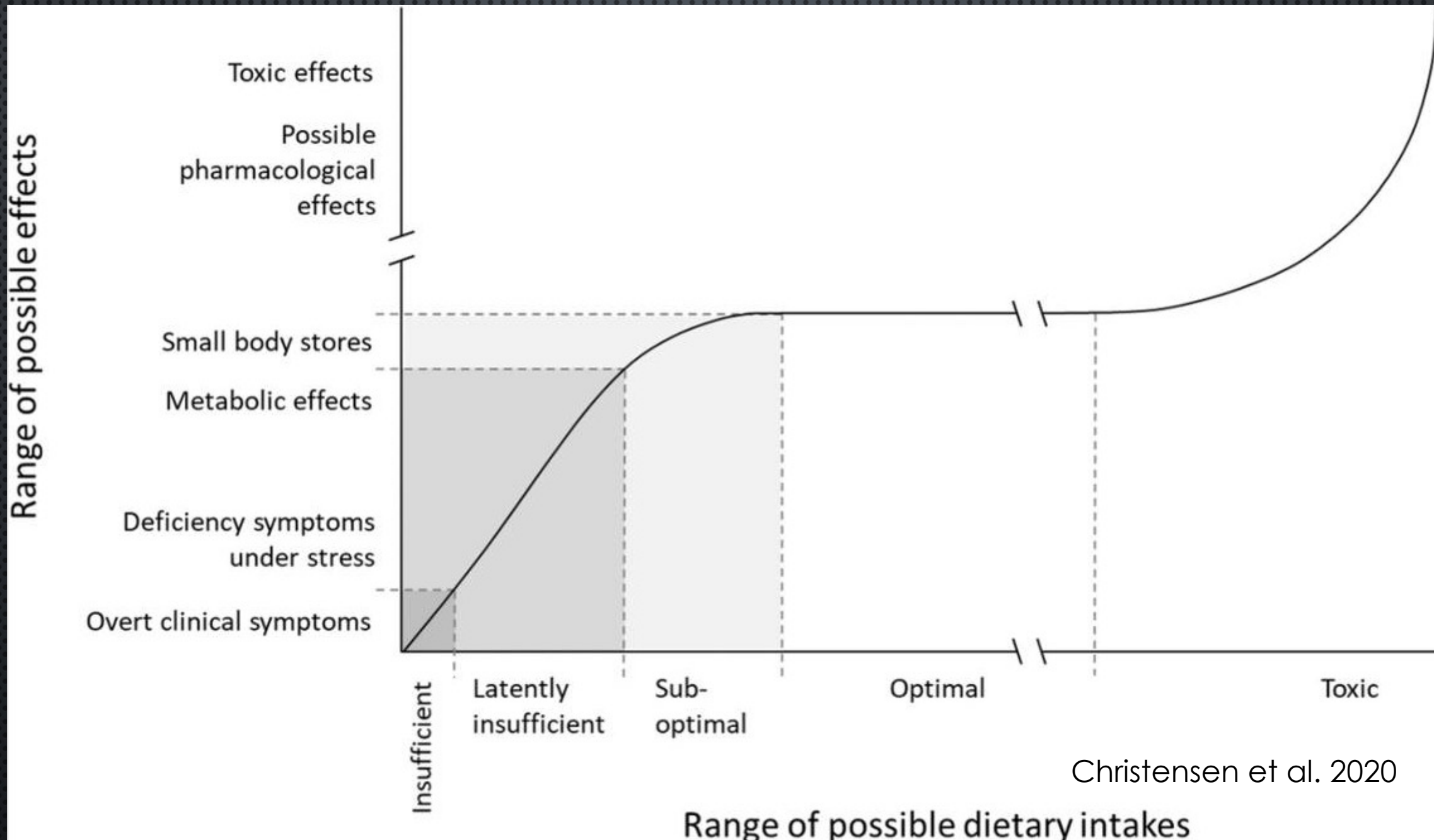


CONCLUSIONS

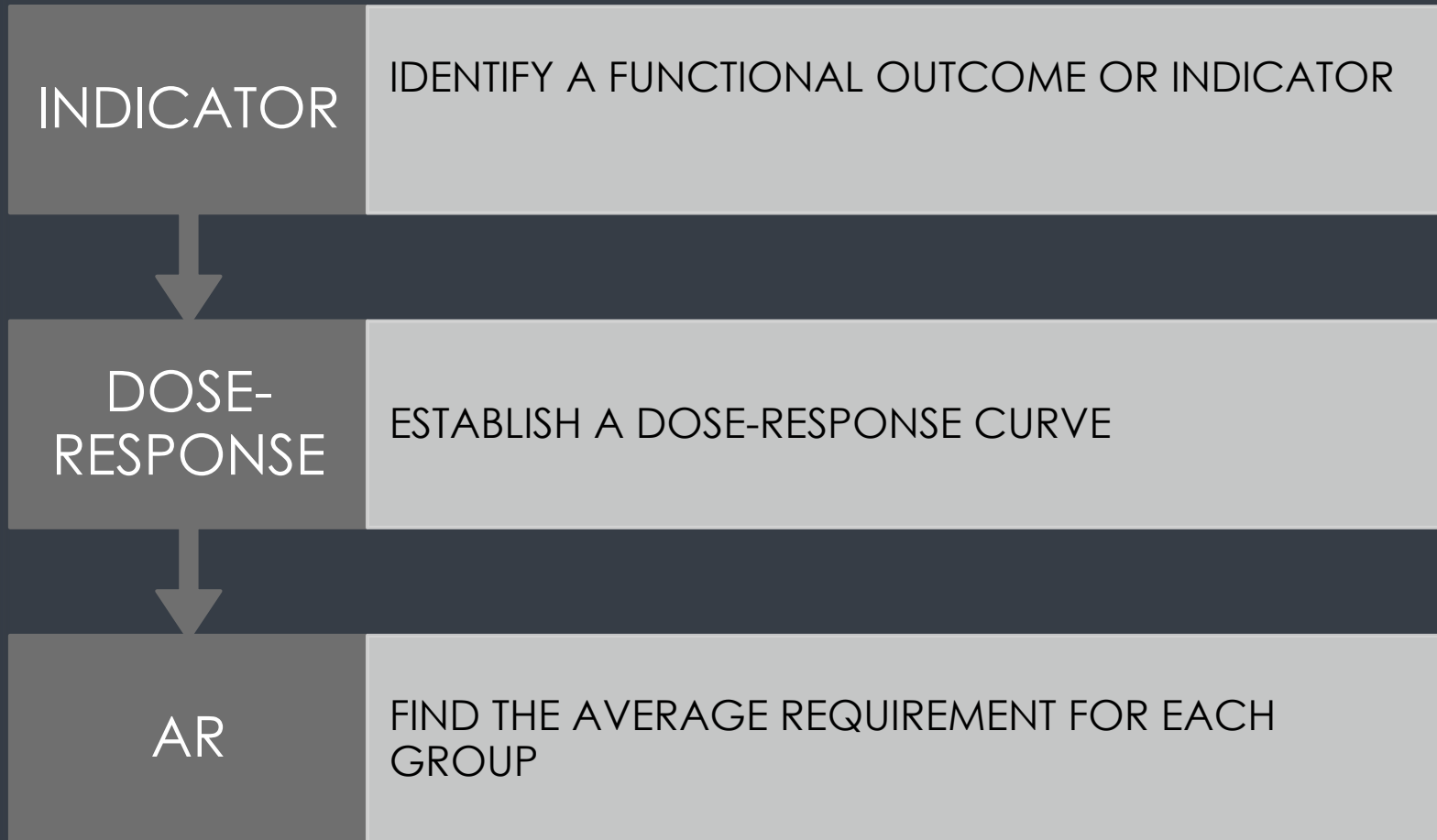
# WHAT IS A NUTRIENT?







# HOW TO DETERMINE A RECOMMENDED INTAKE



BLOMHOFF ET AL. 2023  
CHRISTENSEN ET AL. 2020

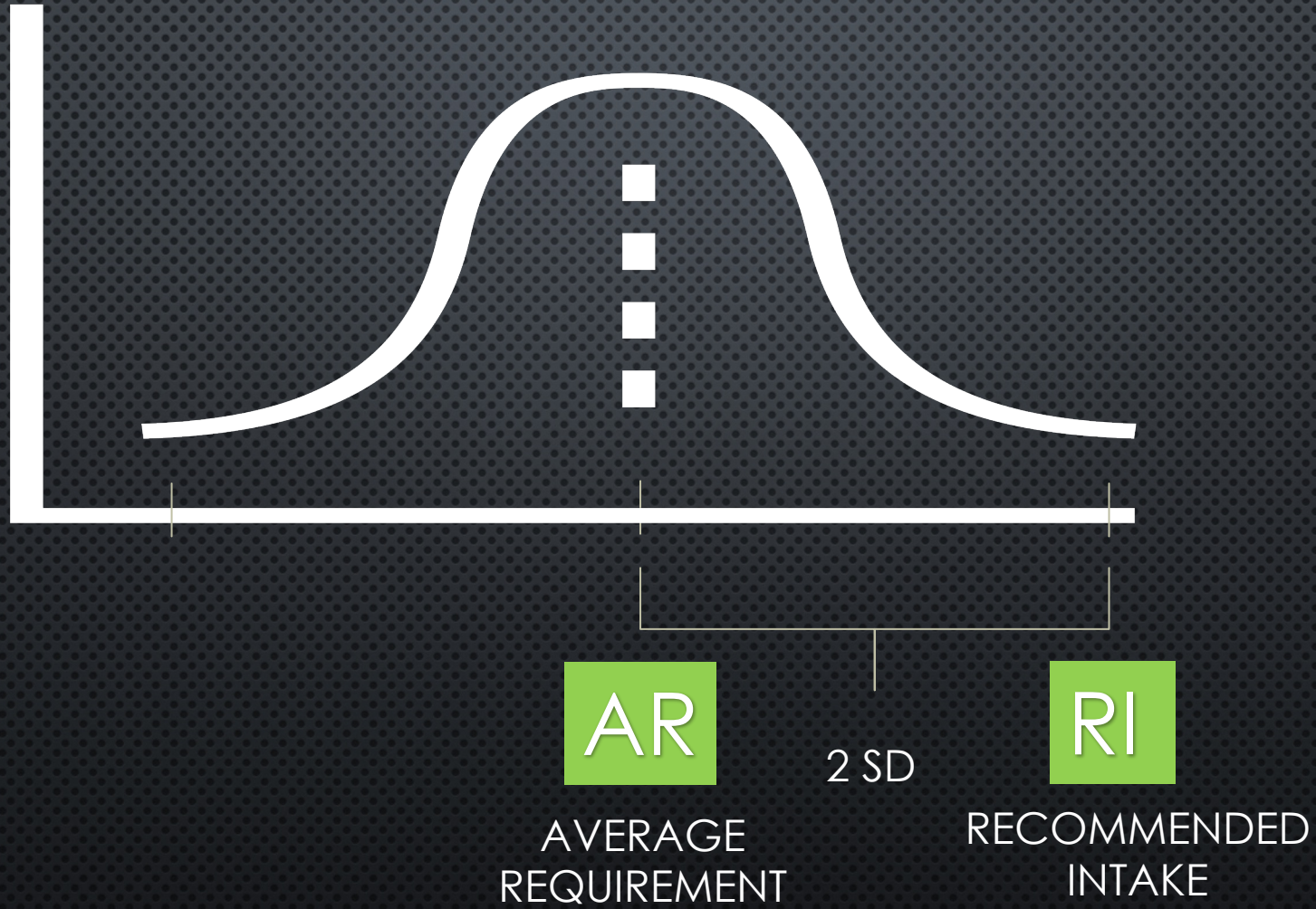
# DIETARY REFERENCE VALUES

- AVERAGE  
REQUIREMENT

MEETS THE DAILY NEED FOR  
50% OF HEALTHY  
INDIVIDUALS

- TOLERABLE  
UPPER INTAKE  
LEVEL

MAXIMUM DAILY  
CONSUMPTION OVER A  
LIFETIME WITHOUT ADVERSE  
HEALTH EFFECTS



# DISPOSITION 45 MINUTES



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CHALLENGES WITH DIETARY REFERENCE VALUES



CUT-OFFS FOR DEFINING DEFICIENCIES AND EXCESS



PUTTING IT TOGETHER WITH SELENIUM



CONCLUSIONS



CHALLENGING  
METHODS TO  
DETERMINE  
NUTRIENT  
REQUIREMENTS

EXPERIMENTAL HUMAN FEEDING STUDIES, BALANCE  
STUDIES

BIOCHEMICAL MARKERS MAY BE USED AS INDICATORS

FACTORIAL METHOD

RISK OF CHRONIC DISEASE

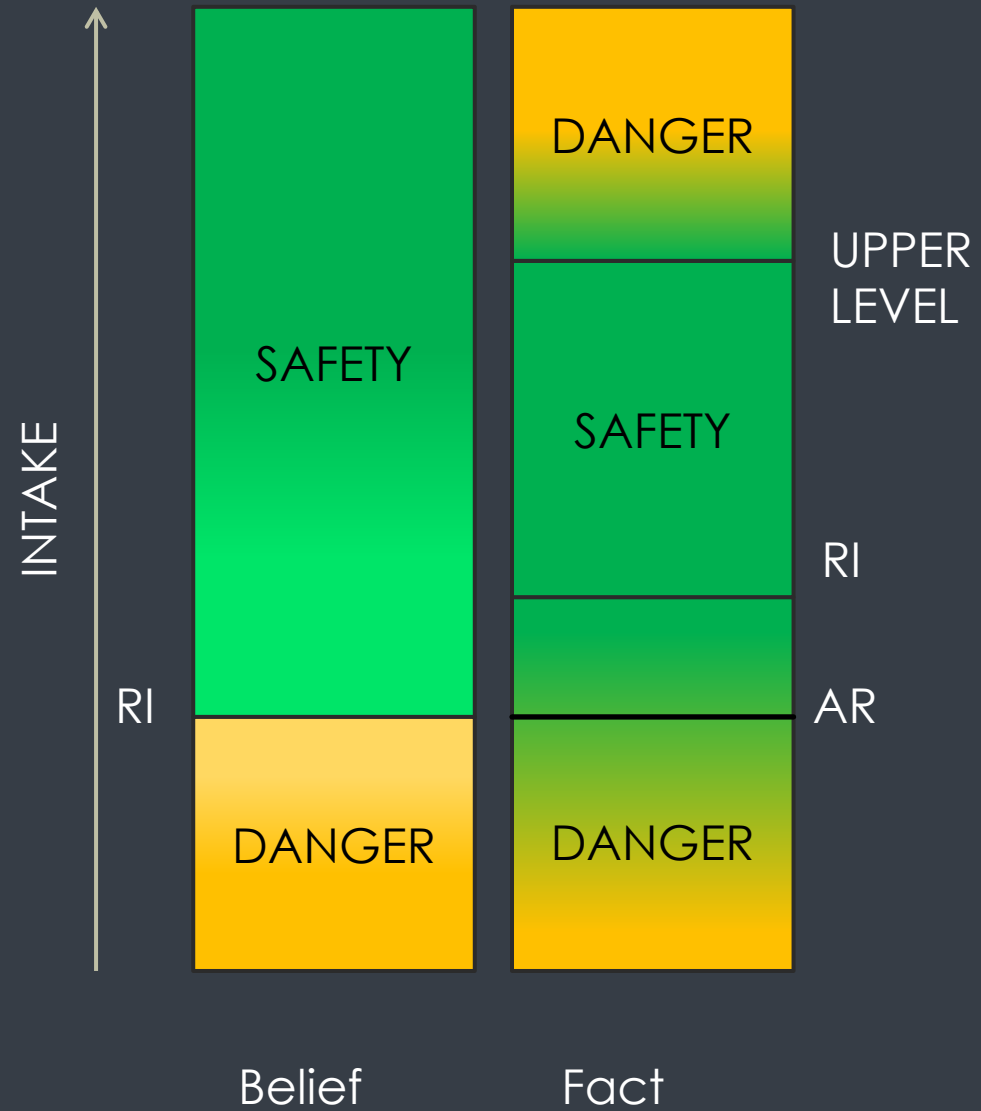
# INFANTS BELOW 6 MONTHS

- NUTRITIONAL REQUIREMENTS = BREAST MILK
- BREASTMILK FROM AN ADEQUATELY NOURISHED WOMAN
- EXCEPT VITAMIN D AND K
- INFANTS WITH BIRTH WEIGHT < 2,5 KG  
1-3 MG/KG/D IRON

# FACTORS AFFECTING NUTRIENT REQUIREMENTS

- HEALTH AND DISEASE
- NUTRIENT INTERACTIONS
- SEX
- WEIGHT AND HEIGHT
- GROWTH
- PREGNANCY
- LACTATION

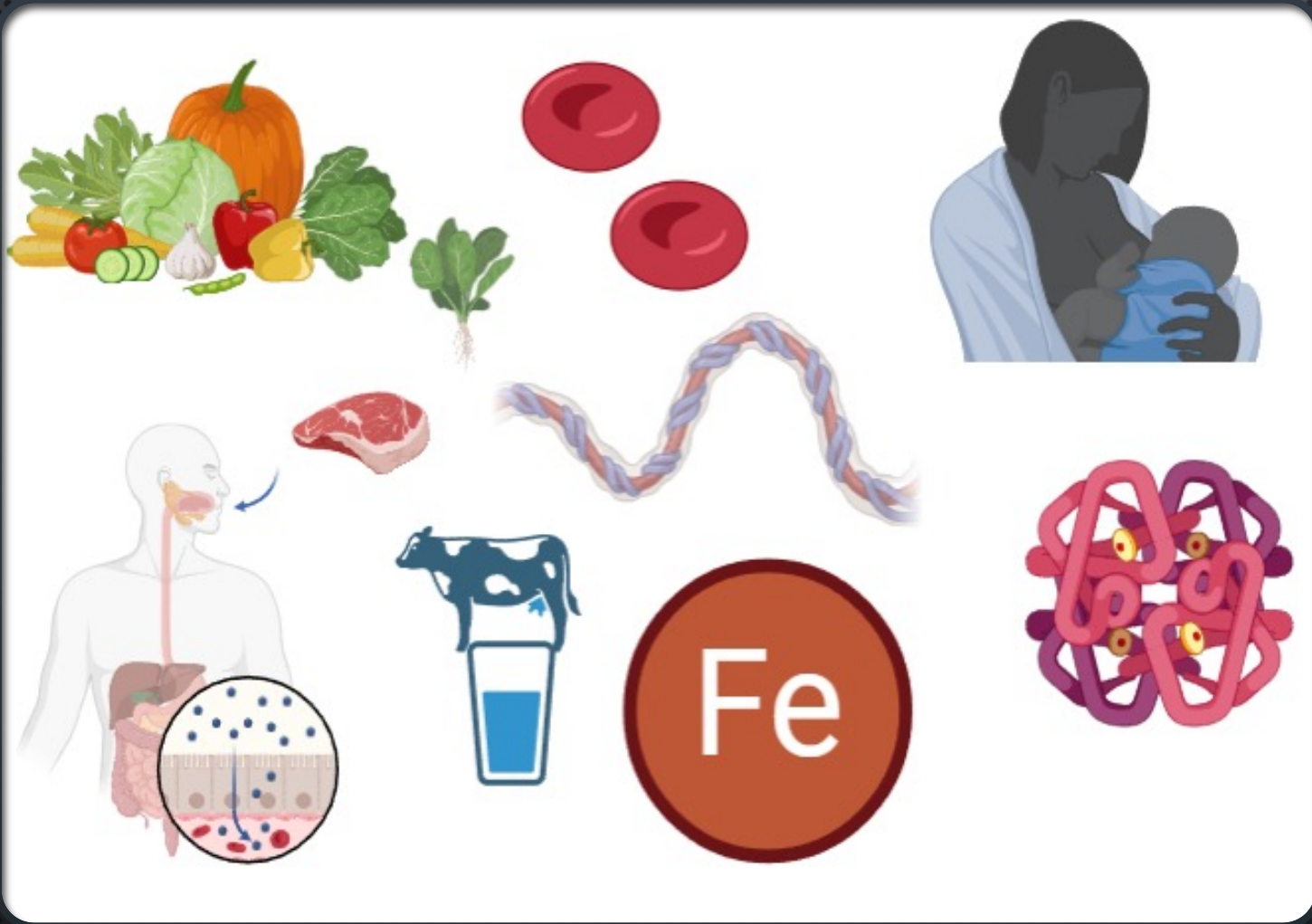
# HOW MUCH IS SAFE?



# IF DOSE- RESPONSE DATA IS NOT AVAILABLE

AI

- ADEQUATE INTAKE = AVERAGE NUTRIENT LEVEL CONSUMED DAILY BY HEALTHY PEOPLE
- EXTRAPOLATION FROM ANOTHER GROUP



# IRON

DOMELLÖF & SJÖBERG 2024  
CREATED WITH BIORENDER.COM

**Table 4.** Iron requirements based on factorial calculations and recommended intakes of iron.

	Weight <sup>c</sup> (kg)	Weight gain (kg/year)	Fe required for growth <sup>d</sup> (mg/day)	Basal iron losses <sup>e</sup> (mg/day)	Menstruation losses of iron (mg/day)	95th percentile	Total requirements of absorbed Fe (mg/day)	Upper limit of variation <sup>f</sup>	Bio- availability (%)	Average iron requirement (mg/day)	Tentative RI (mg/day)	Rounded RI (mg/day)	EFSA 2015 PRI	NNR 2012 RI	IOM 2001
6–12 months <sup>a</sup>	9.0	4.4	0.54	0.20			0.74	0.96	10	7.4	9.6	10	11		11
1–3 years <sup>b</sup>	13.6	2.3	0.26	0.30			0.55	0.72	10	5.5	7.2	7	7	8 <sup>aa</sup>	7
4–6 years <sup>b</sup>	20.7	2.4	0.26	0.25			0.51	0.66	10	5.1	6.6	7	7	8 <sup>aa,bb</sup>	10 <sup>cc</sup>
7–10 years <sup>b</sup>	30.8	3.3	0.36	0.37			0.73	0.94	10	7.3	9.4	9	11	9 <sup>bb</sup>	
11–14 year girls	46.5	4.4	0.46	0.56	0.45	0.89	1.47	1.90	15	9.8	12.7	13	13 <sup>dd</sup>	11	8 <sup>ee</sup>
11–14 year boys	48.2	5.6	0.74	0.58			1.32	1.71	15	8.8	11.4	11	11 <sup>dd</sup>	11	8 <sup>ee</sup>
15–17 year girls	57.9	1.7	0.18	0.69	0.45	1.32	1.32	2.19	15	8.8	14.6	15	13 <sup>dd</sup>	15	15
15–17 year boys	65.6	4.1	0.54	0.79			1.33	1.72	15	8.8	11.49	11	11 <sup>dd</sup>	11	11
Adult men	73.4			1.03			1.03	1.34	15	6.9	8.9	9	11	9	8
Women of repro- ductive age	64.2			0.90	0.45	1.32	1.35	2.22	15	9.0	14.8	15	16	15	18
Postmenopausal women	62.5			0.88			0.88	1.14	15	5.8	7.6	8	11	9	8
Pregnant women	76.4		1.91	1.07			2.98	3.87	15	19.9	25.8	(26) <sup>ff</sup>	16	Suppl	27

# HIGH IRON INTAKE



DIABETES?

CANCER?

POOR VISUAL-MOTOR INTEGRATION?

UPPER INTAKE LEVEL 60 MG PER DAY

ACUTE OVERDOSE >20 MG/KG



# DISPOSITION 45 MINUTES



ORGANIZATIONS



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DIETARY REFERENCE VALUES



CUT-OFFS FOR DEFINING DEFICIENCIES AND  
EXCESS



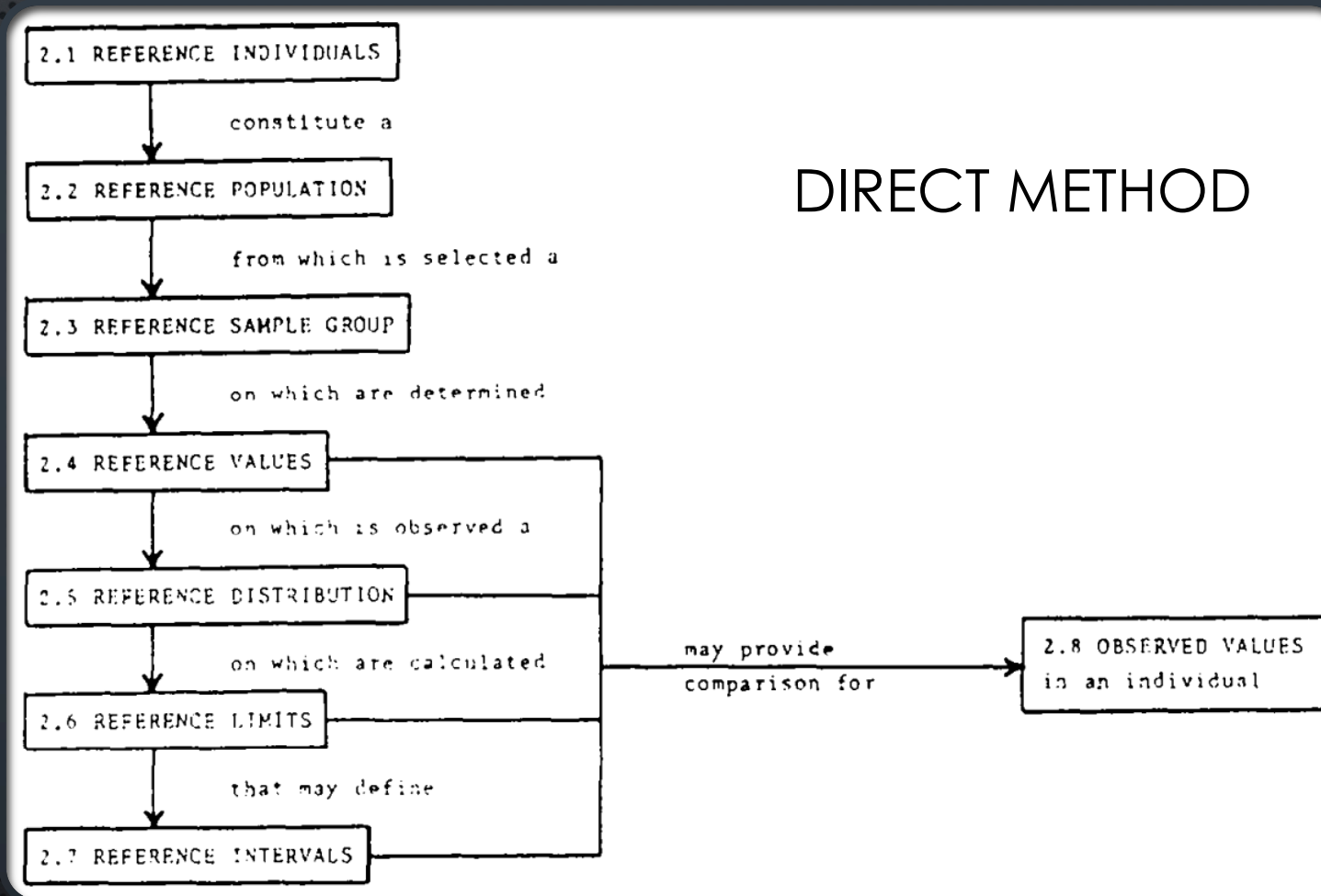
PUTTING IT TOGETHER WITH SELENIUM

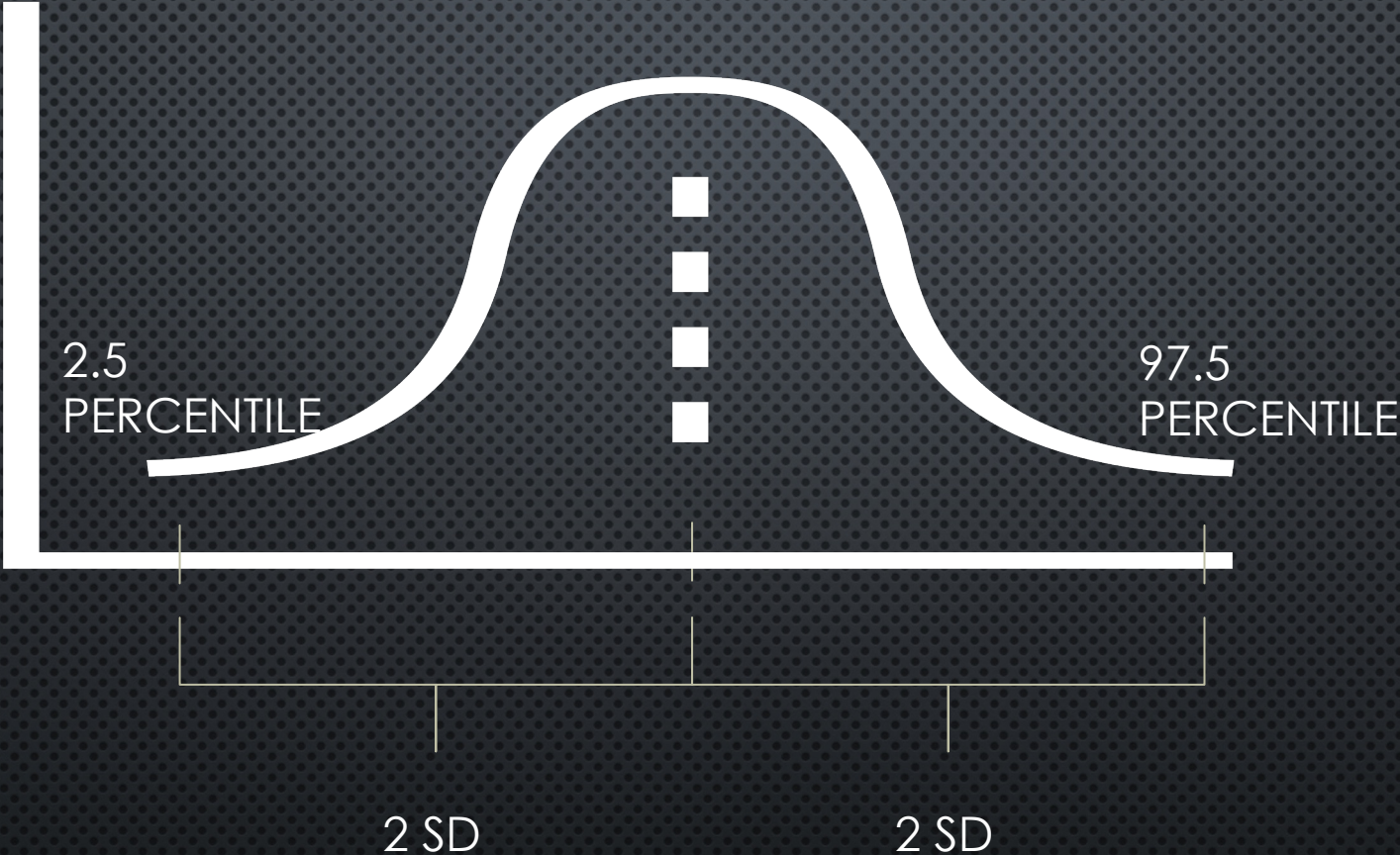


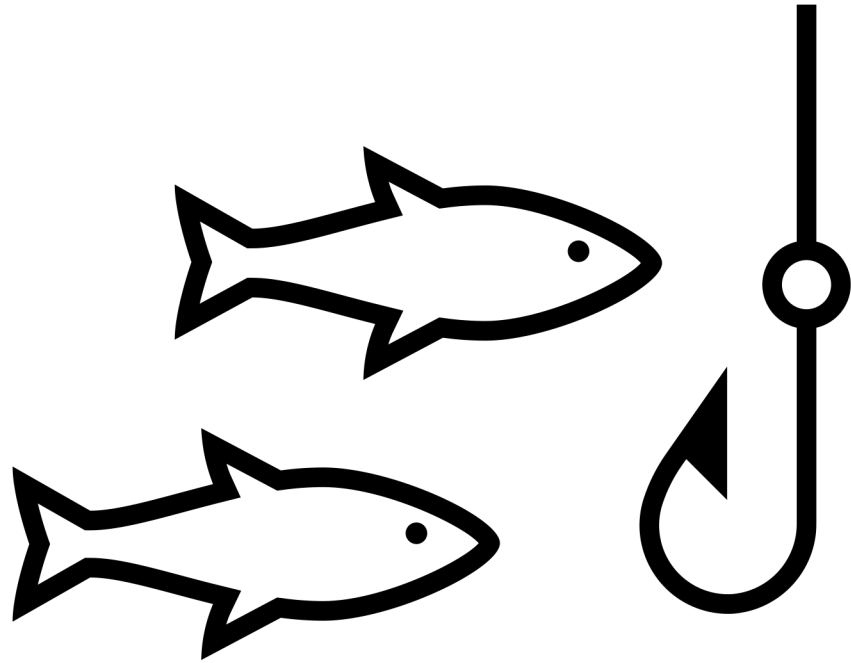
CONCLUSIONS

# CUT-OFFS FOR DEFINING DEFICIENCY AND EXCESS IN CHILDREN

## DIRECT METHOD







IF YOU ARE  
FISHING IN A  
POND....

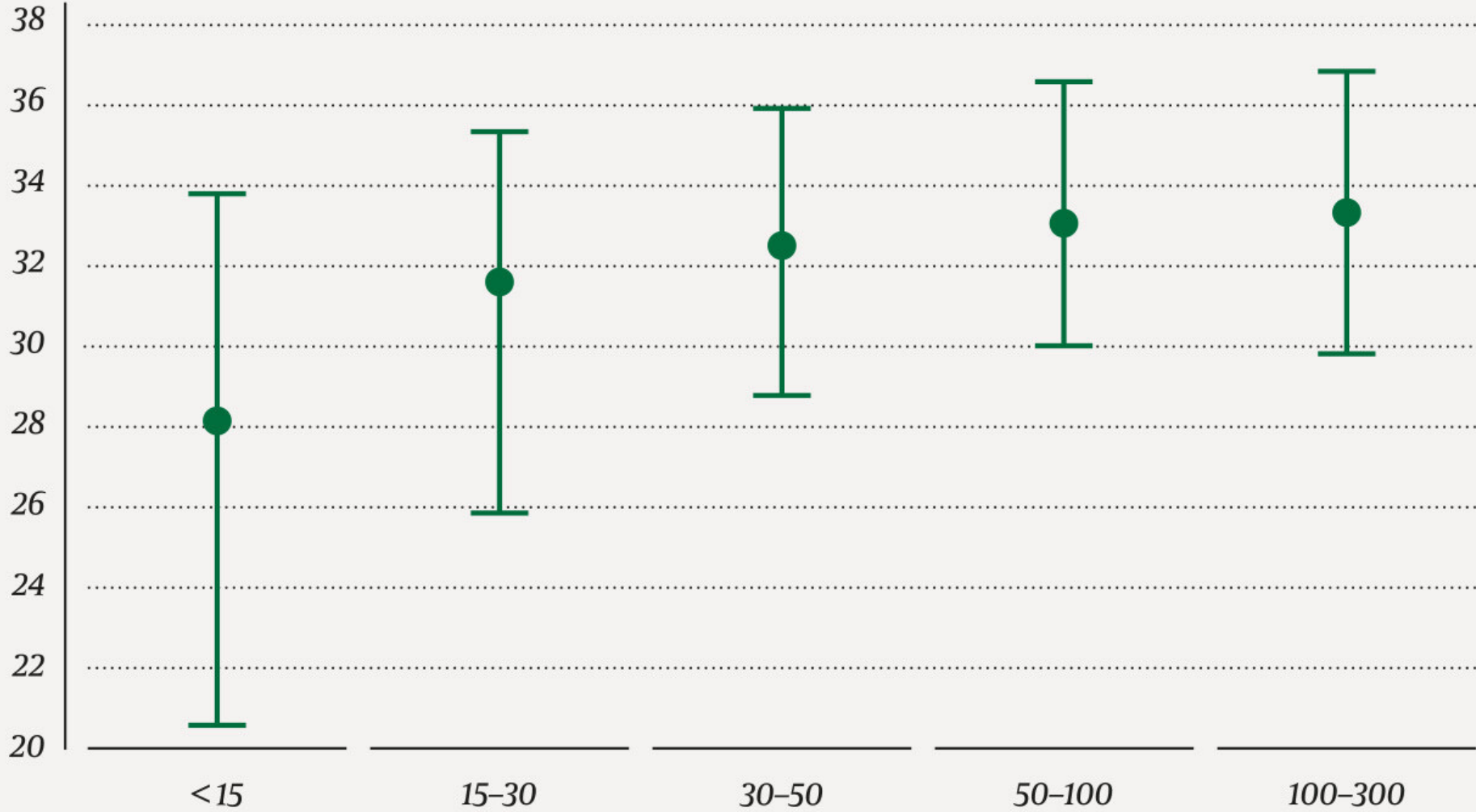
95%  
REFERENCE  
INTERVALS  
AND  
POPULATIONS

NORWAY  
5-29 NMOL/L

USA  
16-109 NMOL/L

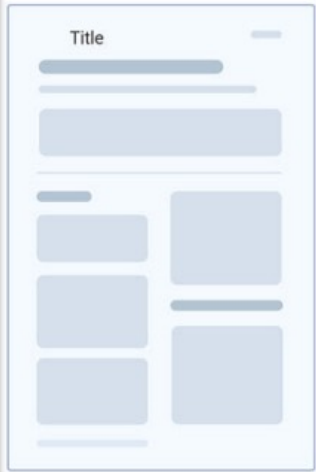
SCHWETTMANN & BERBU 2015  
PFEIFFER ET AL. 2015

Hb i retikulocytter (pg)



S-ferritin (µg/l)

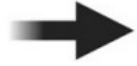
Bjørke-Monsen &  
Lillemoen 2019



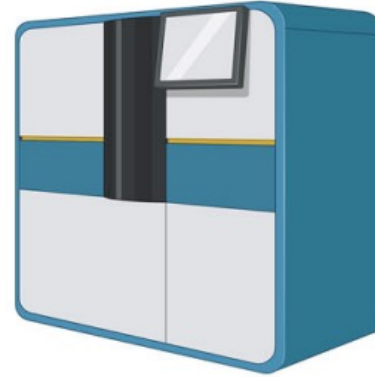
Planning and  
pre-collection



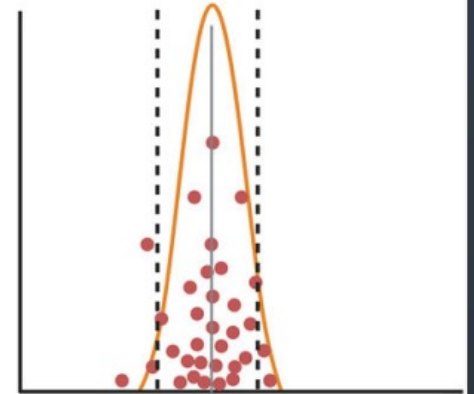
Patient  
preparation  
and collection



Specimen  
processing



Specimen  
testing



Data  
collection  
and analysis

# DIRECT METHOD

# DIRECT METHOD

Resource-intensive

Expensive

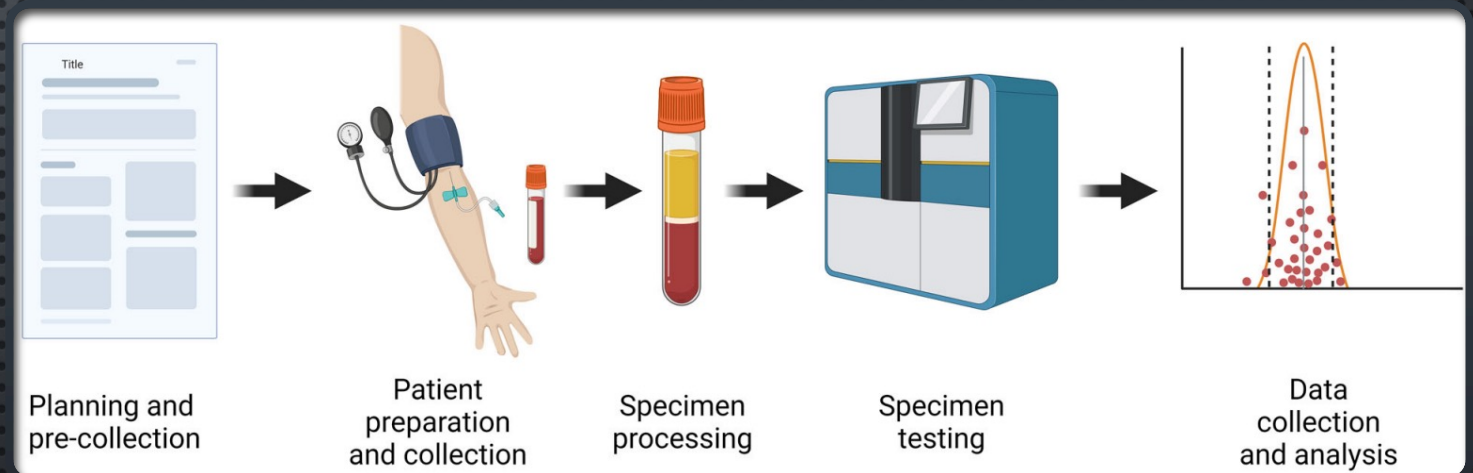
Volunteers

Selection bias

Subjects truly healthy?

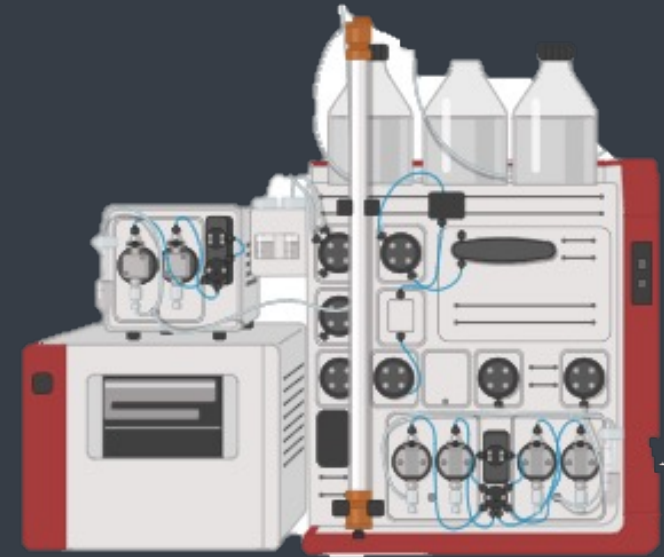
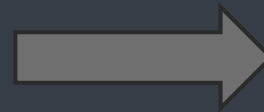
Ethics

Sample volume



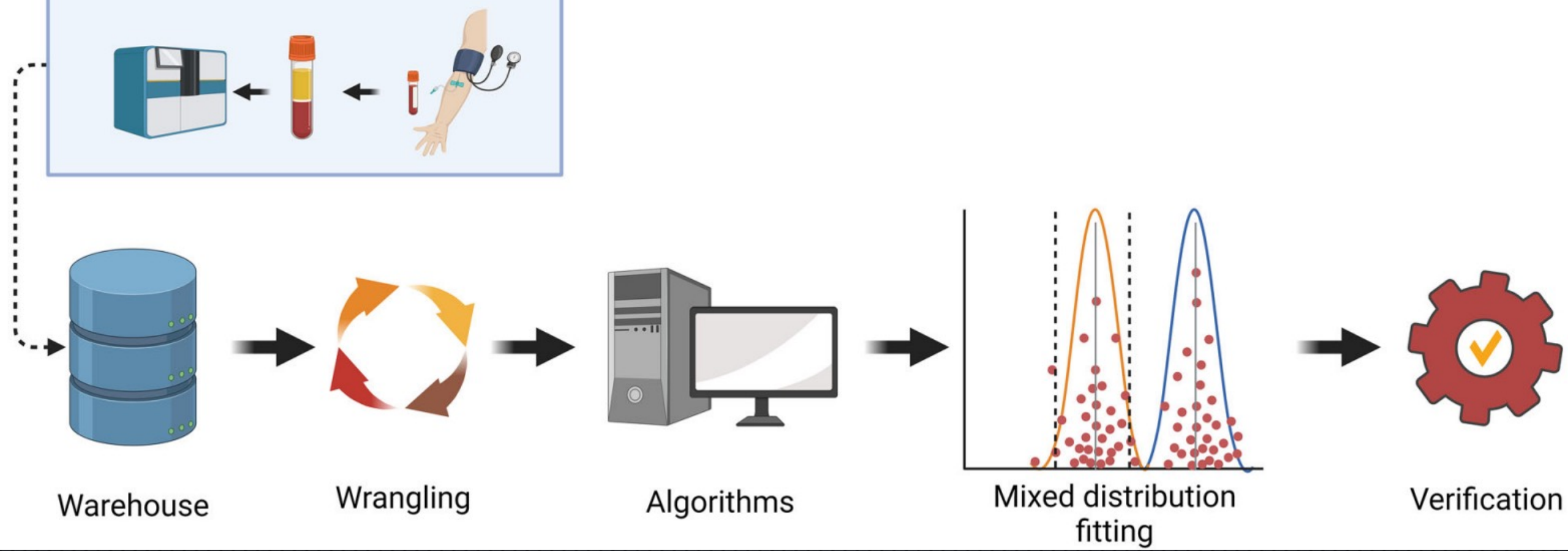


VERIFICATION  
AND  
TRANSFERENCE



CREATED WITH BIORENDER.COM

DOYLE & BUNCH 2023

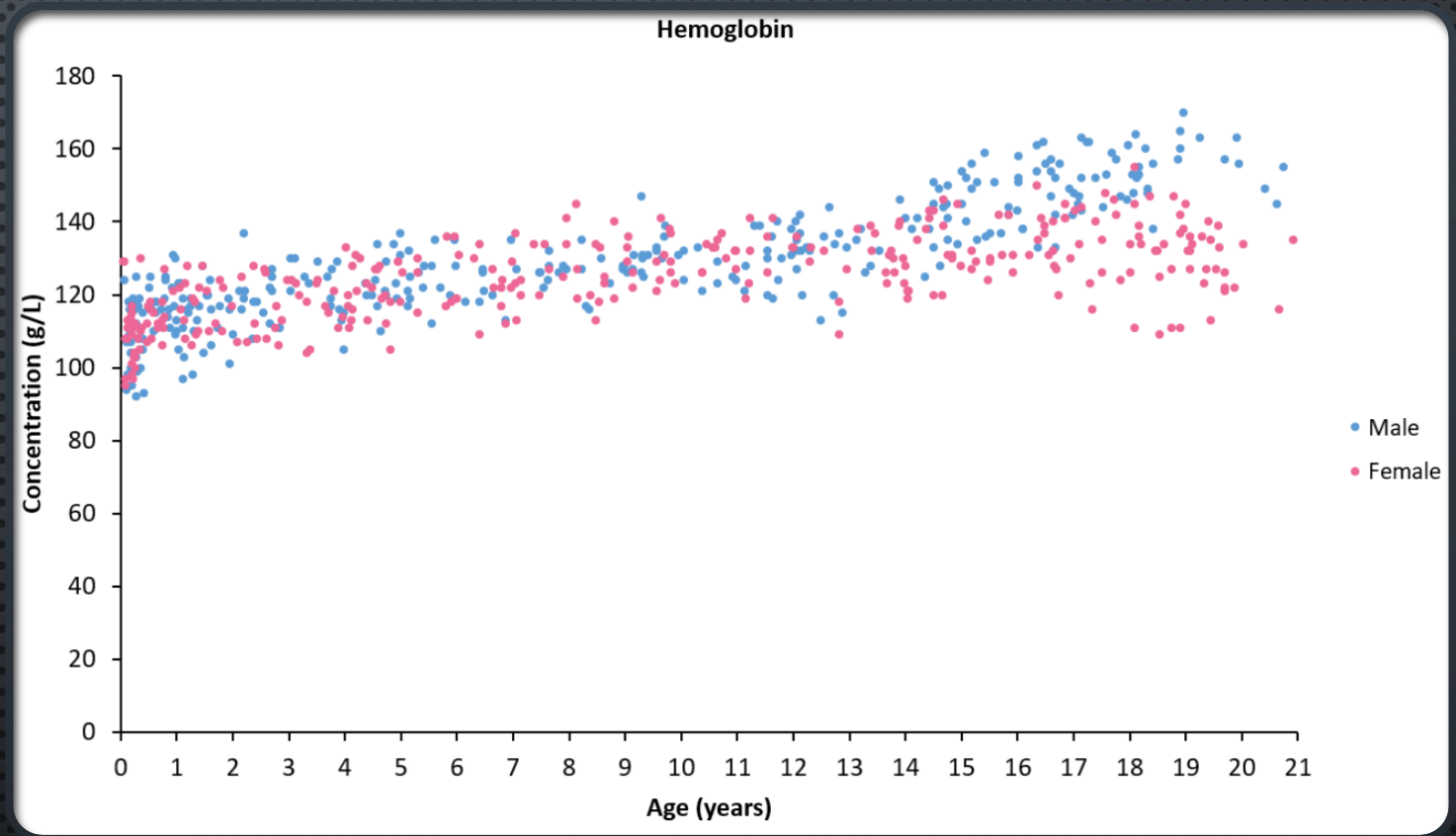


# INDIRECT METHOD

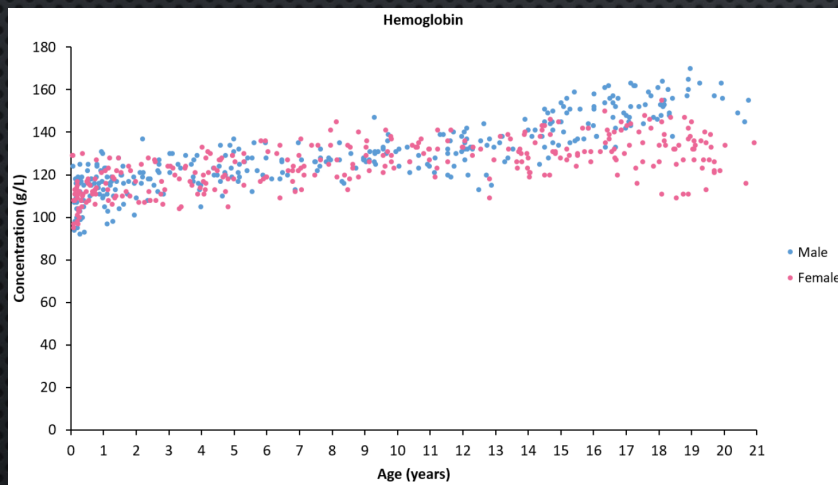
DOYLE & BUNCH 2023

CONTINUOUS  
REFERENCE  
INTERVALS

# Hemoglobin



# CONTINUOUS REFERENCE INTERVALS

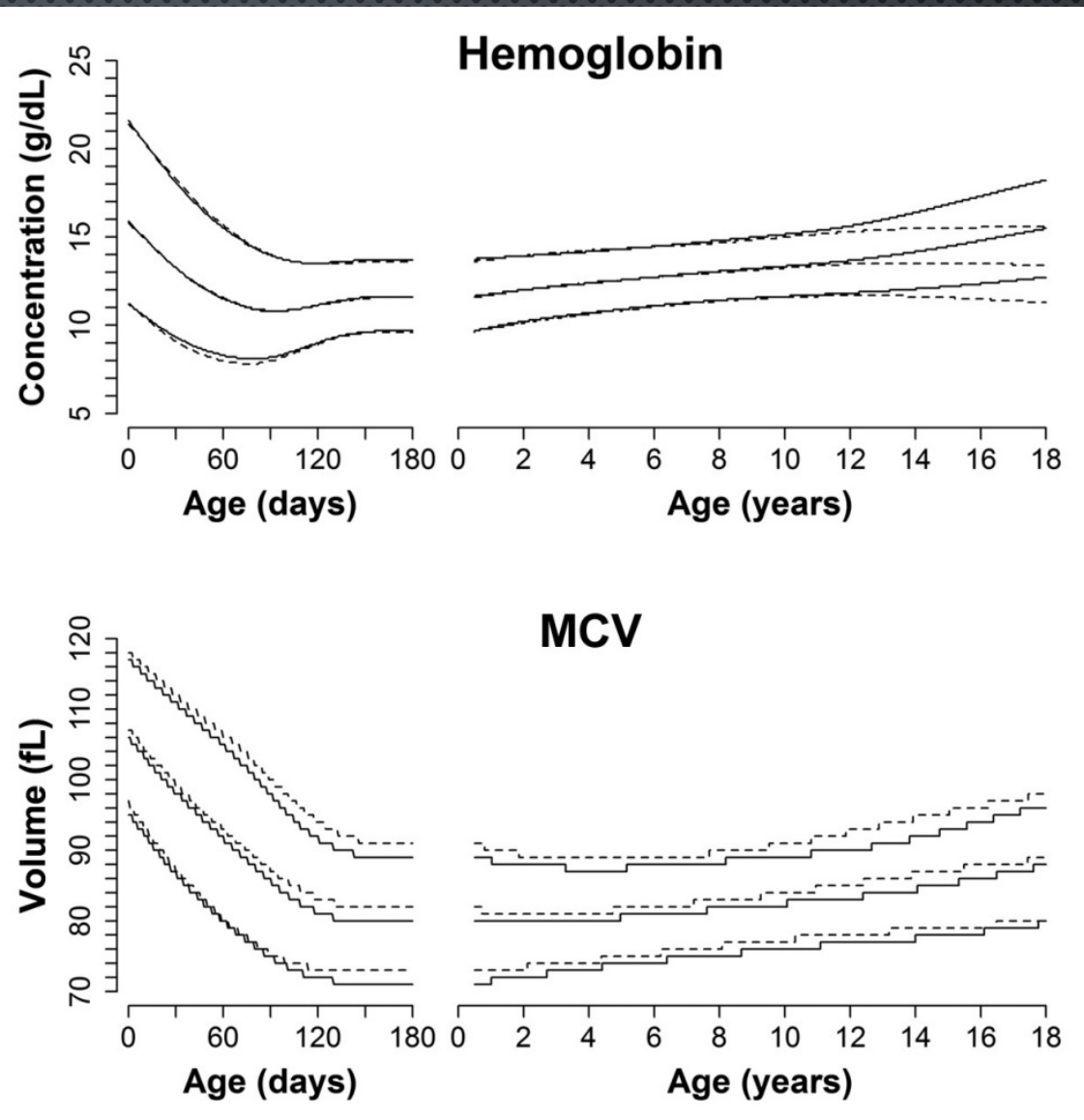
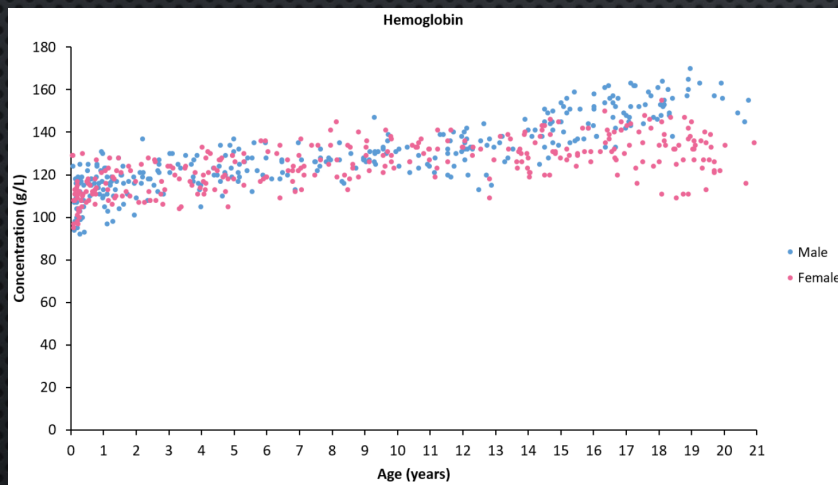


Age	Lower Limit	Upper Limit	Sample Size	Lower Confidence Intervals	Higher Confidence Intervals
0 to <1 Years	93.4	129	94	(90.3,96.0)	(127, 132)
1 to <4 Years	100	132	105	(97.6,103)	(130, 134)
4 to <14 Years	112	141	247	(109, 113)	(140, 146)
14 to <21 Years	112	151	99	(107, 115)	(148, 154)

## Male Reference Intervals

Age	Lower Limit	Upper Limit	Sample Size	Lower Confidence Intervals	Higher Confidence Intervals
0 to <1 Years	93.4	129	94	(90.3,96.0)	(127, 132)
1 to <4 Years	100	132	105	(97.6,103)	(130, 134)
4 to <14 Years	112	141	247	(109, 113)	(140, 146)
14 to <21 Years	129	167	89	(126, 132)	(164, 170)

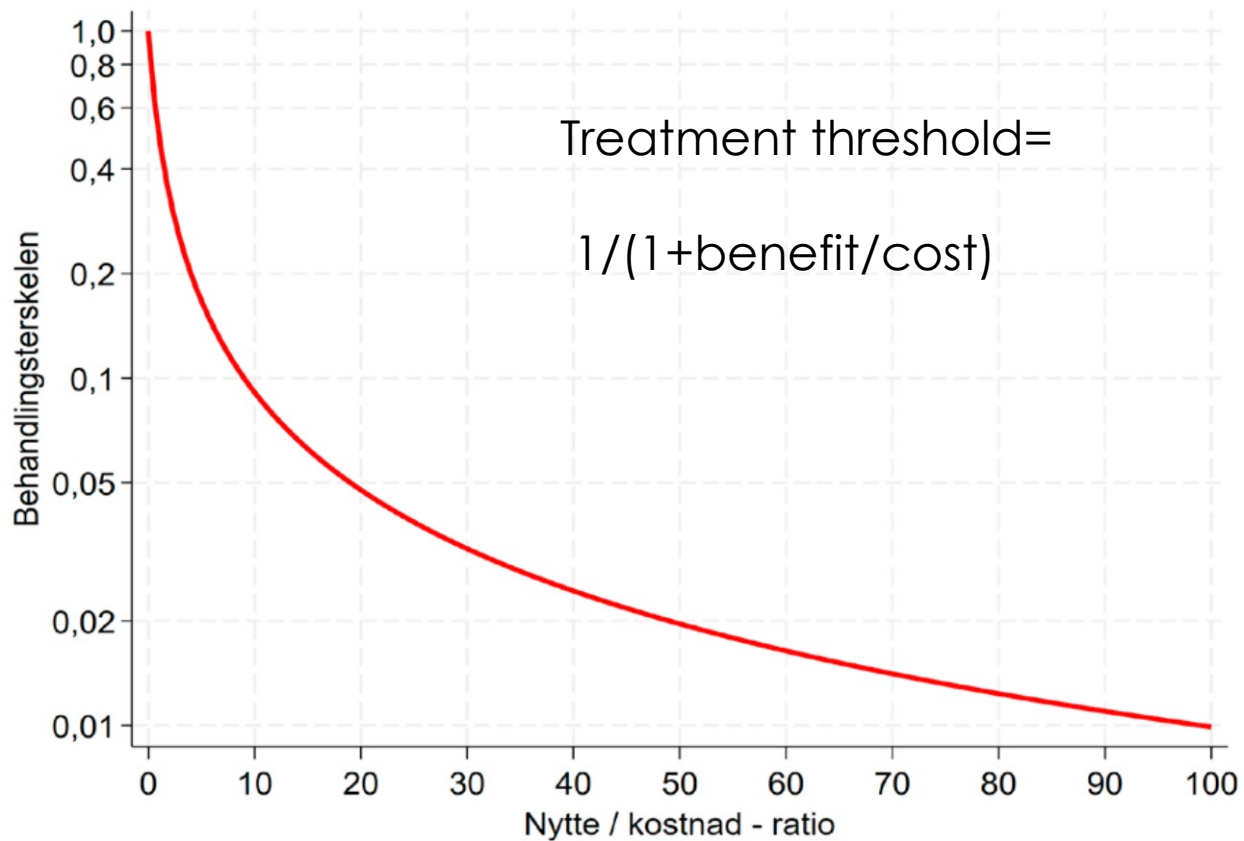
# CONTINUOUS REFERENCE INTERVALS





# COST-BENEFIT ANALYSES THERAPEUTIC THRESHOLDS

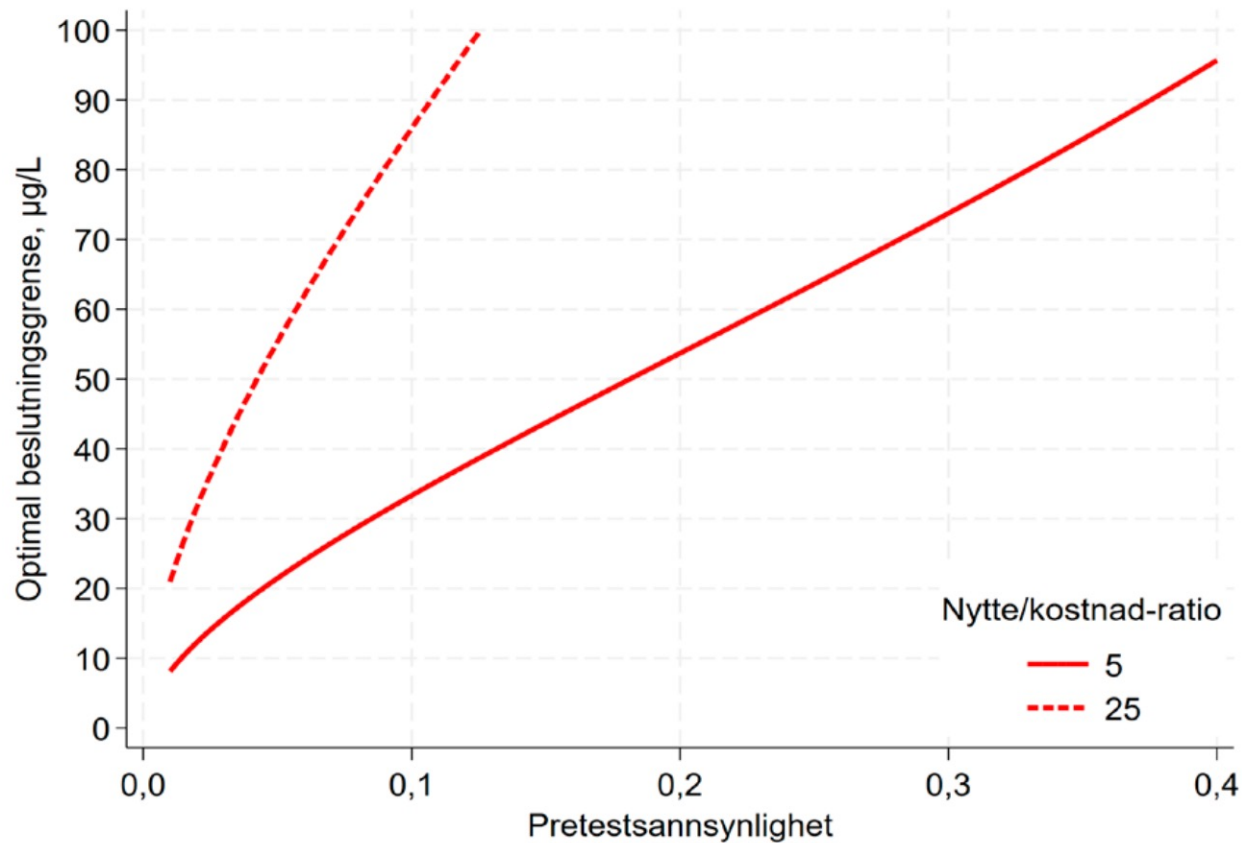
PAUKER ET AL. 1975



# TREATMENT THRESHOLD

PAUKER ET AL. 1975

ÅSBERG & HOF 2023



# OPTIMAL TREATMENT THRESHOLD

ÅSBERG & HOF 2023



# DISPOSITION 45 MINUTES



ORGANIZATIONS



DEFINITIONS



DIETARY REFERENCE VALUES



CUT-OFFS FOR DEFINING DEFICIENCIES AND  
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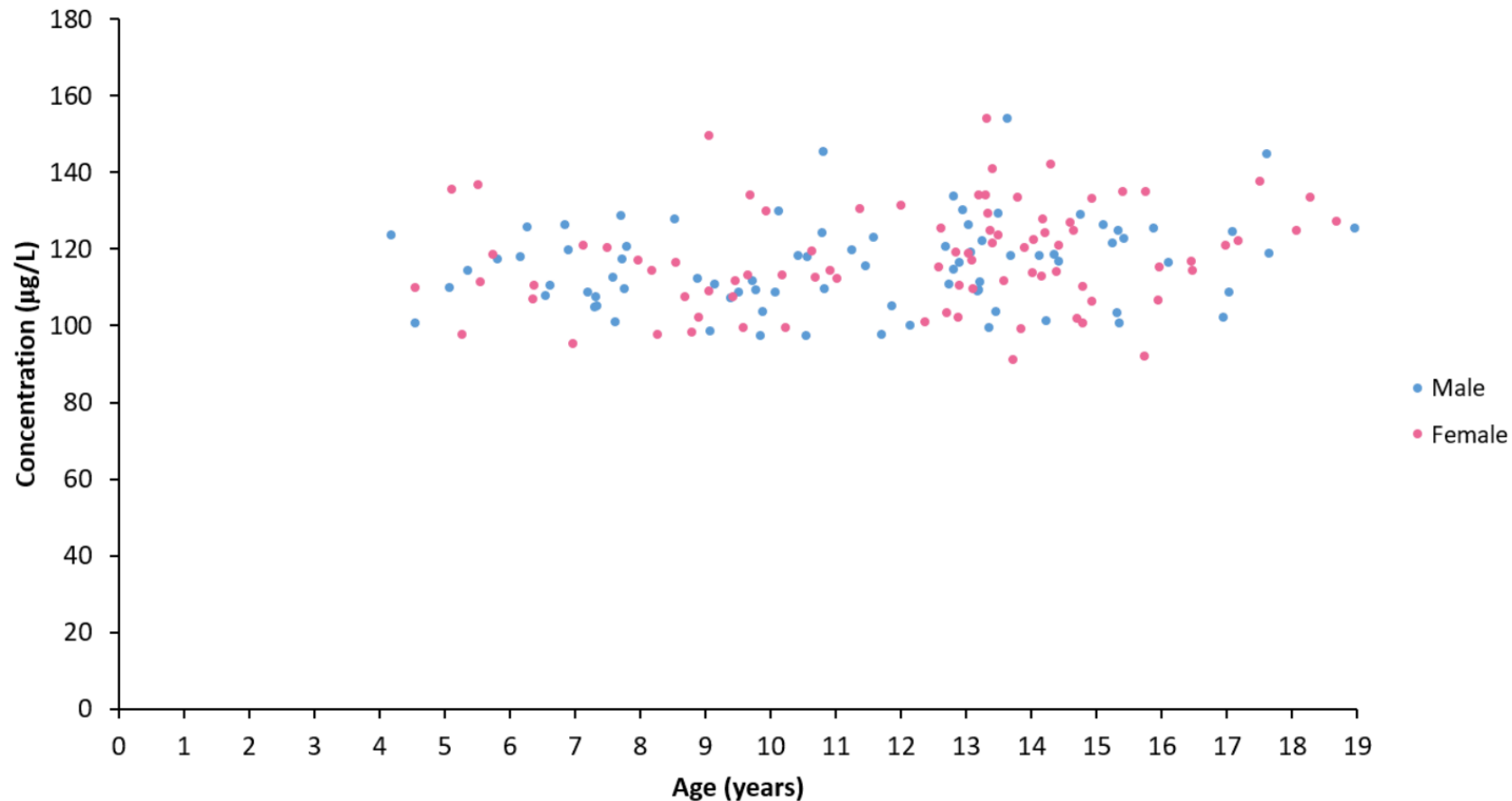


PUTTING IT TOGETHER WITH SELENIUM



CONCLUSIONS

### Selenium (Plasma)

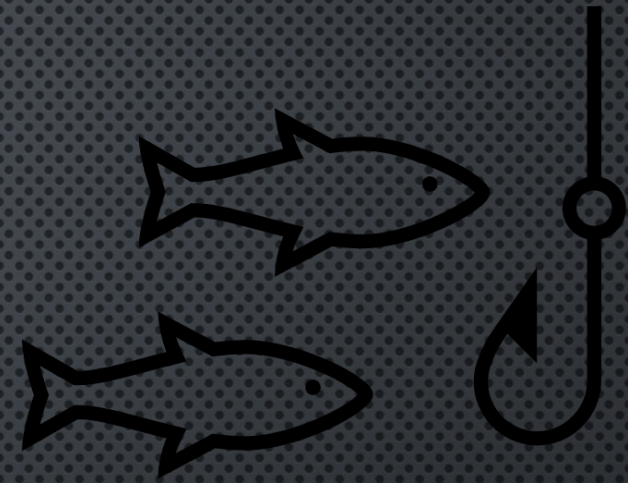


CALIPERDATABASE.ORG

### Reference Intervals (Female and Male)

Age	Lower Limit	Upper Limit	Sample Size	Lower Confidence Intervals	Higher Confidence Intervals
4 to <19 Years	1.24 µmol/L 97.6	1.85 µmol/L 145.5	166	(91.1, 98.4)	(136.9, 154.2)

Aldersgruppe	$\mu\text{mol/L}$
6 md.:	0,6–1,2
0–1 år:	0,2–1,4
2–5 år:	0,4–1,6
6–17 år:	0,5–1,5



CALIPERDATABASE.ORG  
 BRUKERHANDBOKEN.NO  
 HURST ET AL: 2010

### Reference Intervals (Female and Male)

Age	Lower Limit	Upper Limit	Sample Size	Lower Confidence Intervals	Higher Confidence Intervals
4 to <19 Years	1.24 $\mu\text{mol/L}$ 97.6	1.85 $\mu\text{mol/L}$ 145.5	166	(91.1, 98.4)	(136.9, 154.2)

# SELENIUM

Animal  
food  
products  
Plant  
foods  
Nuts

Intake

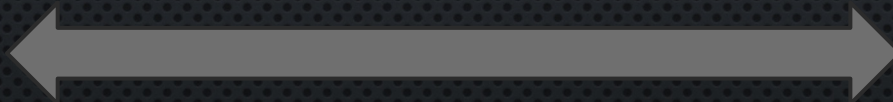


Saturation  
of Seleno-  
protein in  
plasma

Indicator



Health



- Antioxidant enzymes
- Thyroid hormones
- Neurological development

- Selenosis
- Neurological development

# DISPOSITION 45 MINUTES



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PUTTING IT TOGETHER WITH SELENIUM



CONCLUSIONS

# CONCLUSIONS

- CORE REFERENCE VALUES  
AR AND UL
- INDICATORS
- REFERENCE INTERVALS
- DECISION LIMITS
- STUDIES ON CHILDREN
- HARMONIZATION



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THANK YOU FOR YOUR ATTENTION!

Q & A