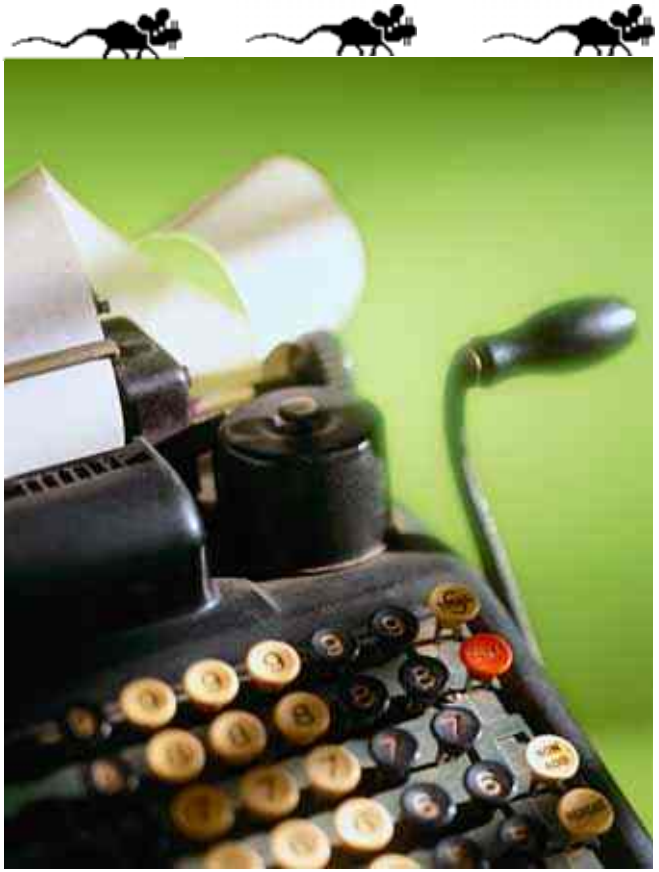
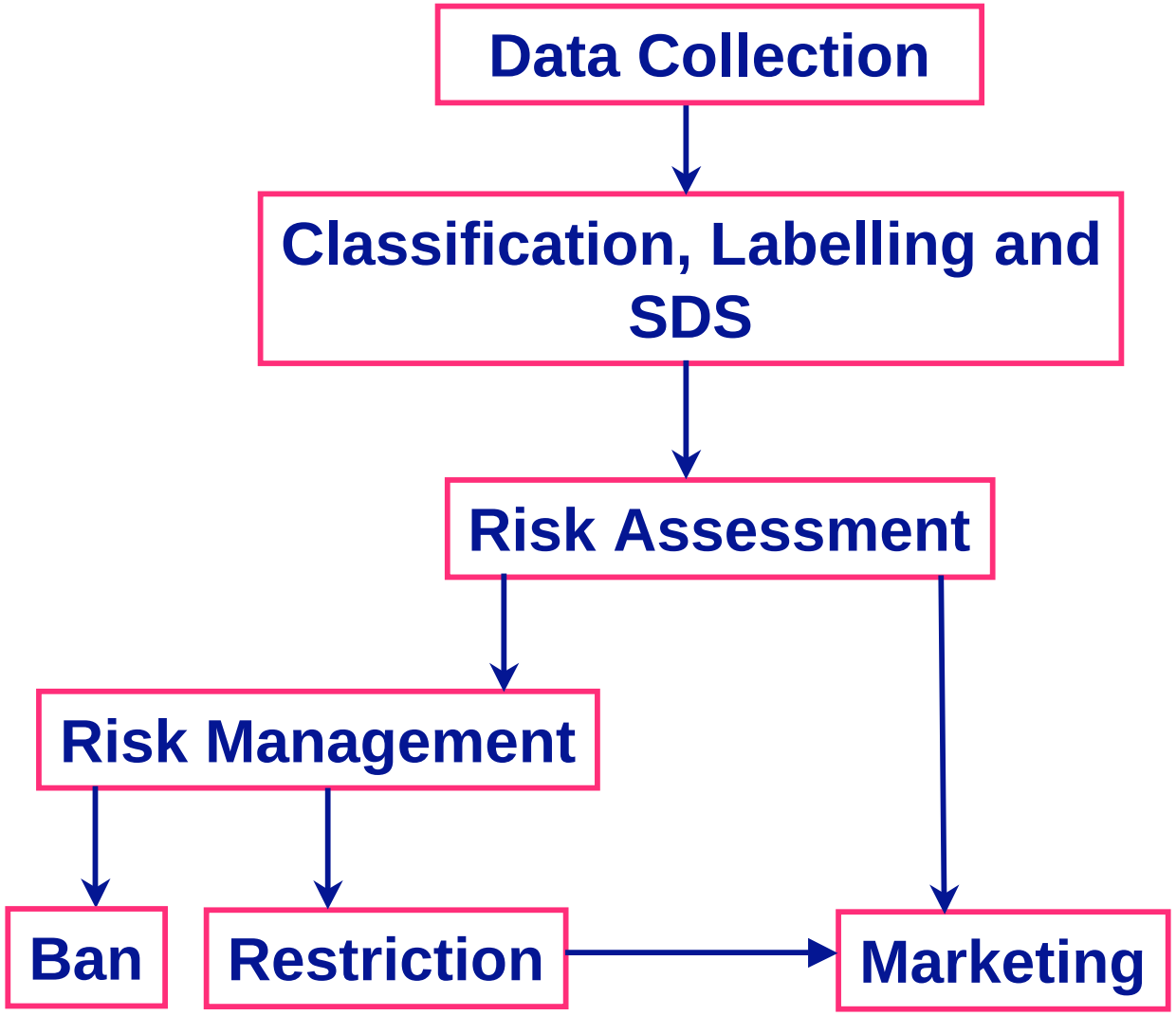
european consensus platform on 3R-alternatives



Ecopa REACH Animal Use Calculator

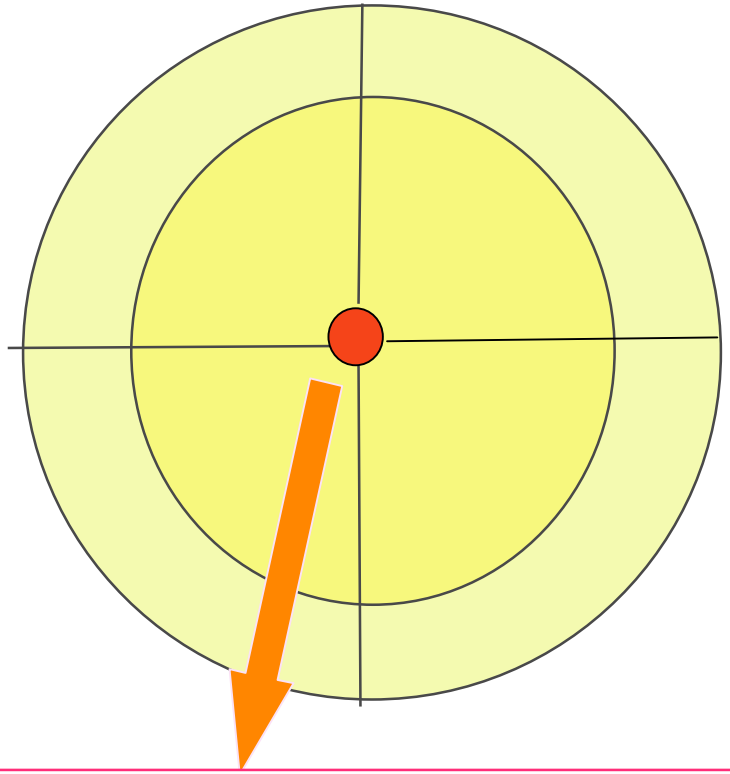
Karsten Müller &
Simon Webb

Apply the Same Principle as Today...



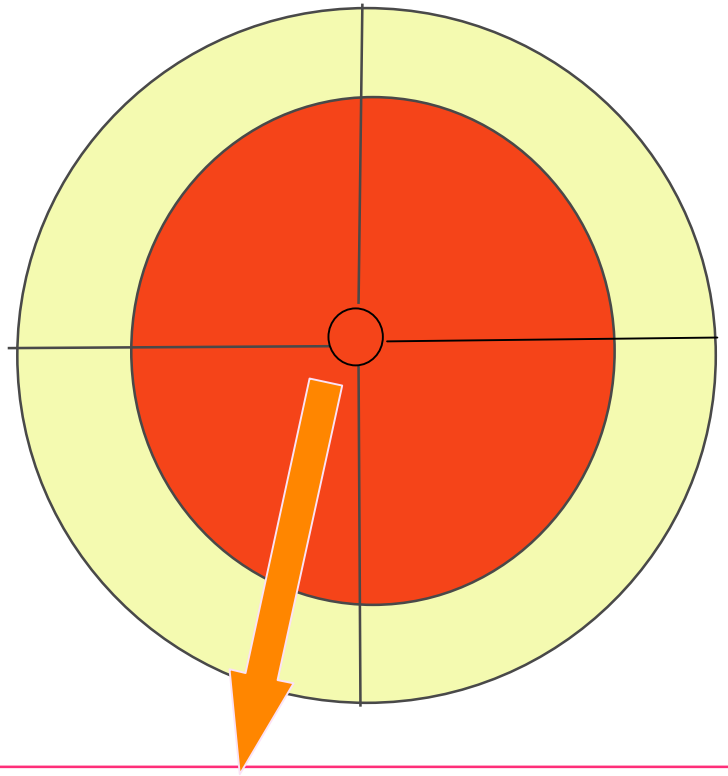
…but Bigger Scope…

Today



~3,000 new substances in the EU
~140 existing chemicals (>1000t/y)
Regulatory Evaluation
3,140 substances

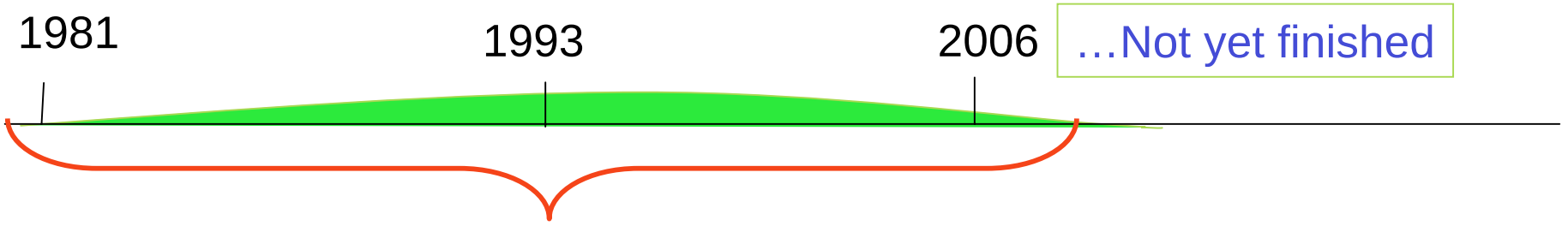
REACH



New and existing substances
>1t/y/manufacturer or importer
Regulatory Evaluation
30,000 substances

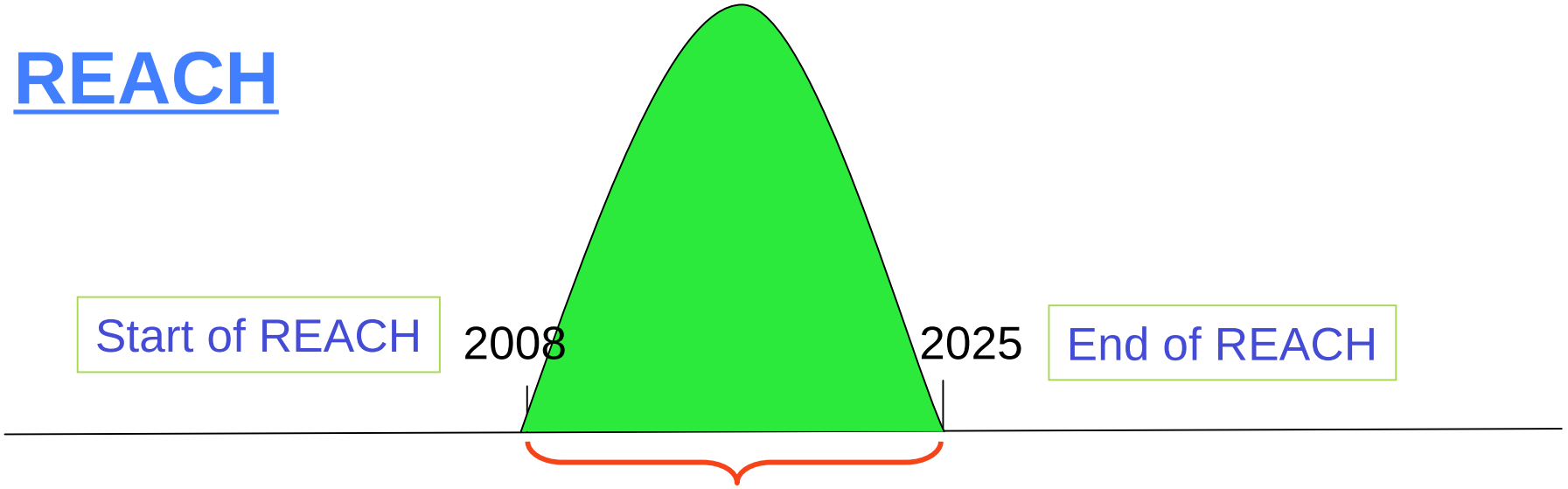
…and Much Quicker…

Until now



25 years for 3,140 substances

REACH

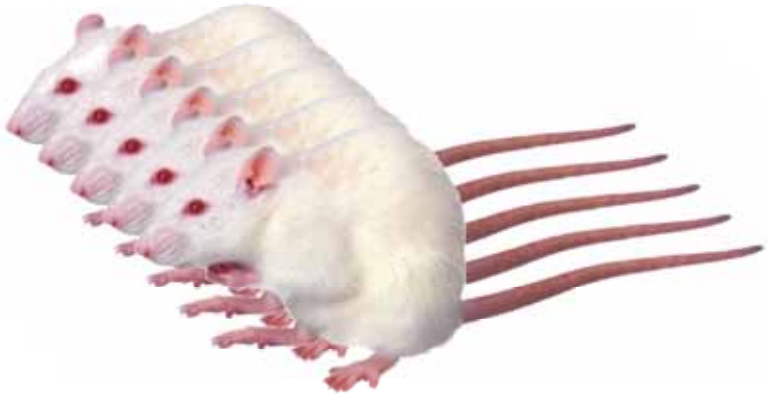


17 years for 30,000 substances

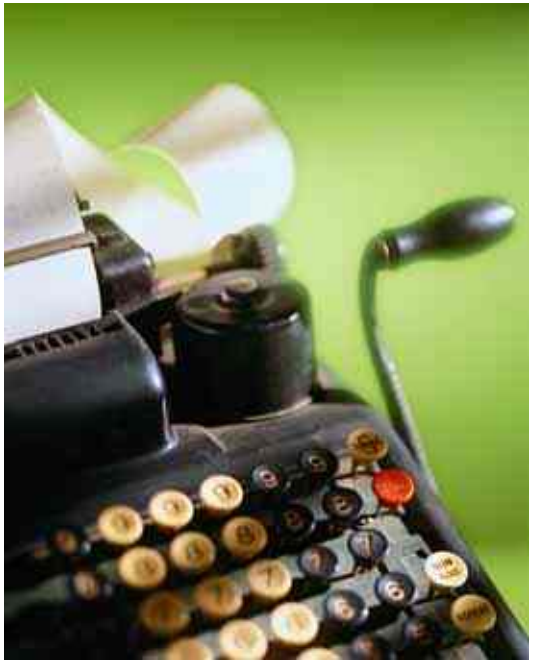
...and has Sparked a Debate!

Principle of the Calculator

REACH
Test Requirements



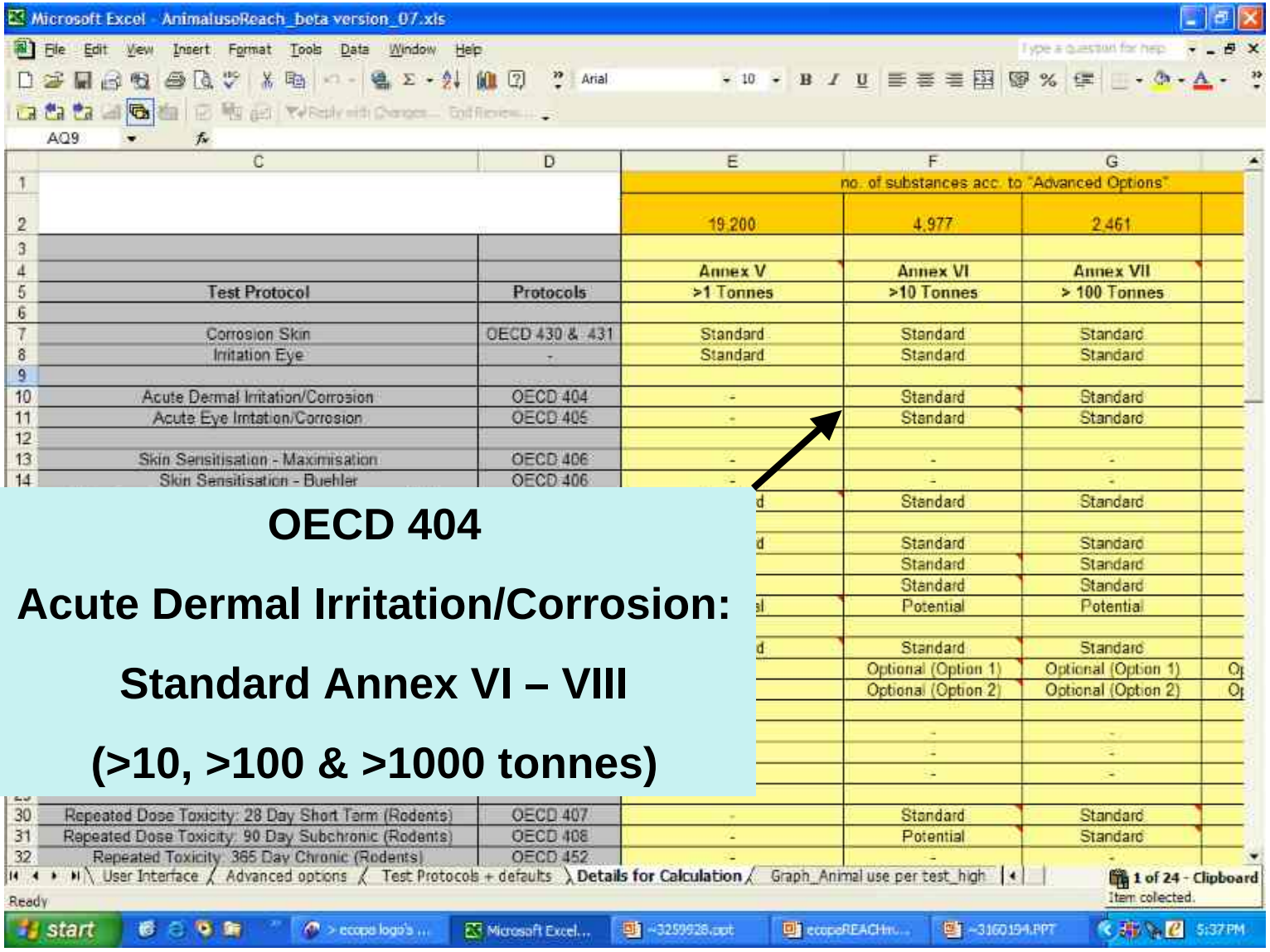
Test
Protocols



Availability of
Existing Data

Projected
Need to Test

REACH Test Requirements



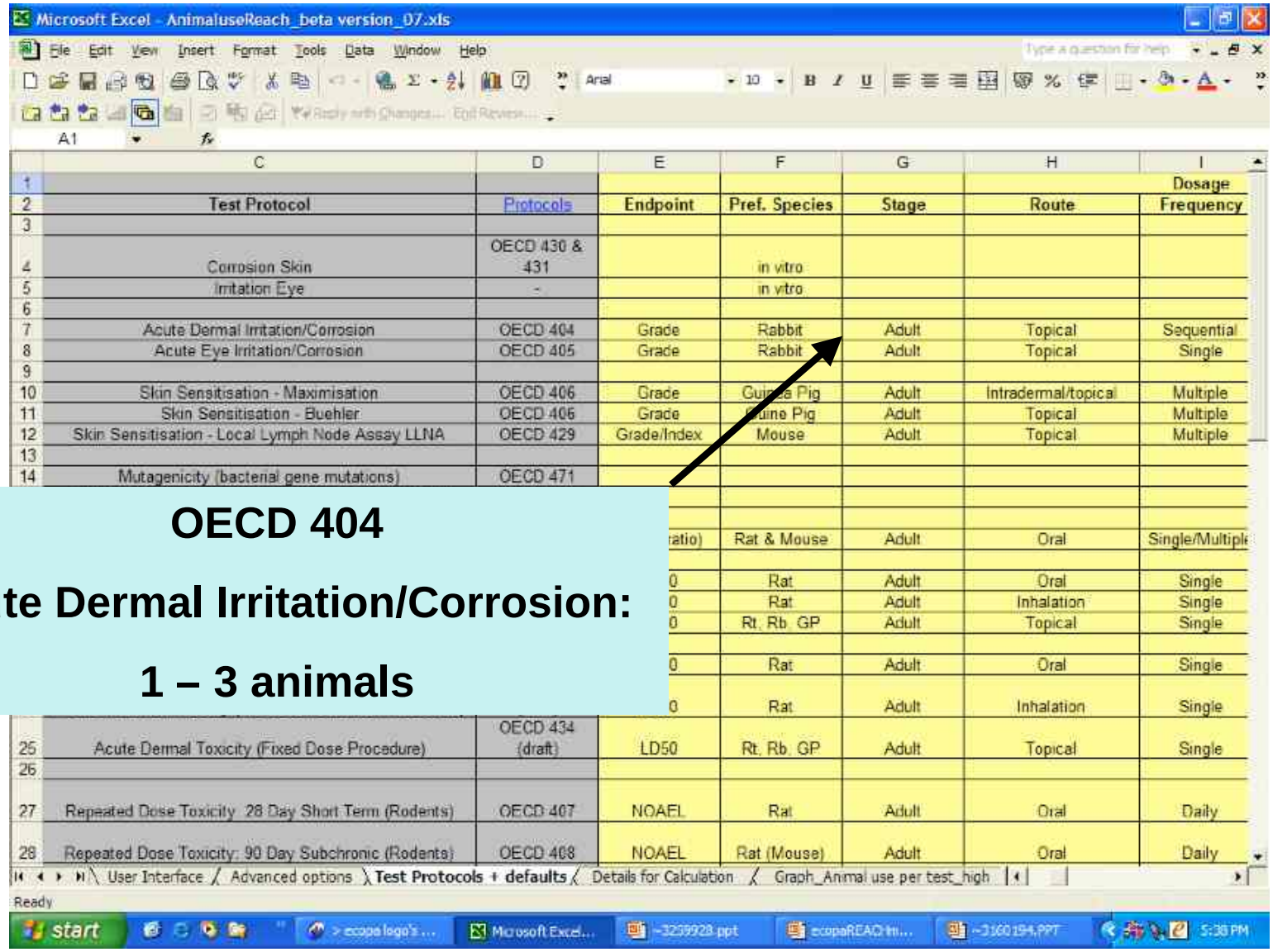
OECD 404

Acute Dermal Irritation/Corrosion:

Standard Annex VI – VIII

(>10, >100 & >1000 tonnes)

OECD Test Protocols

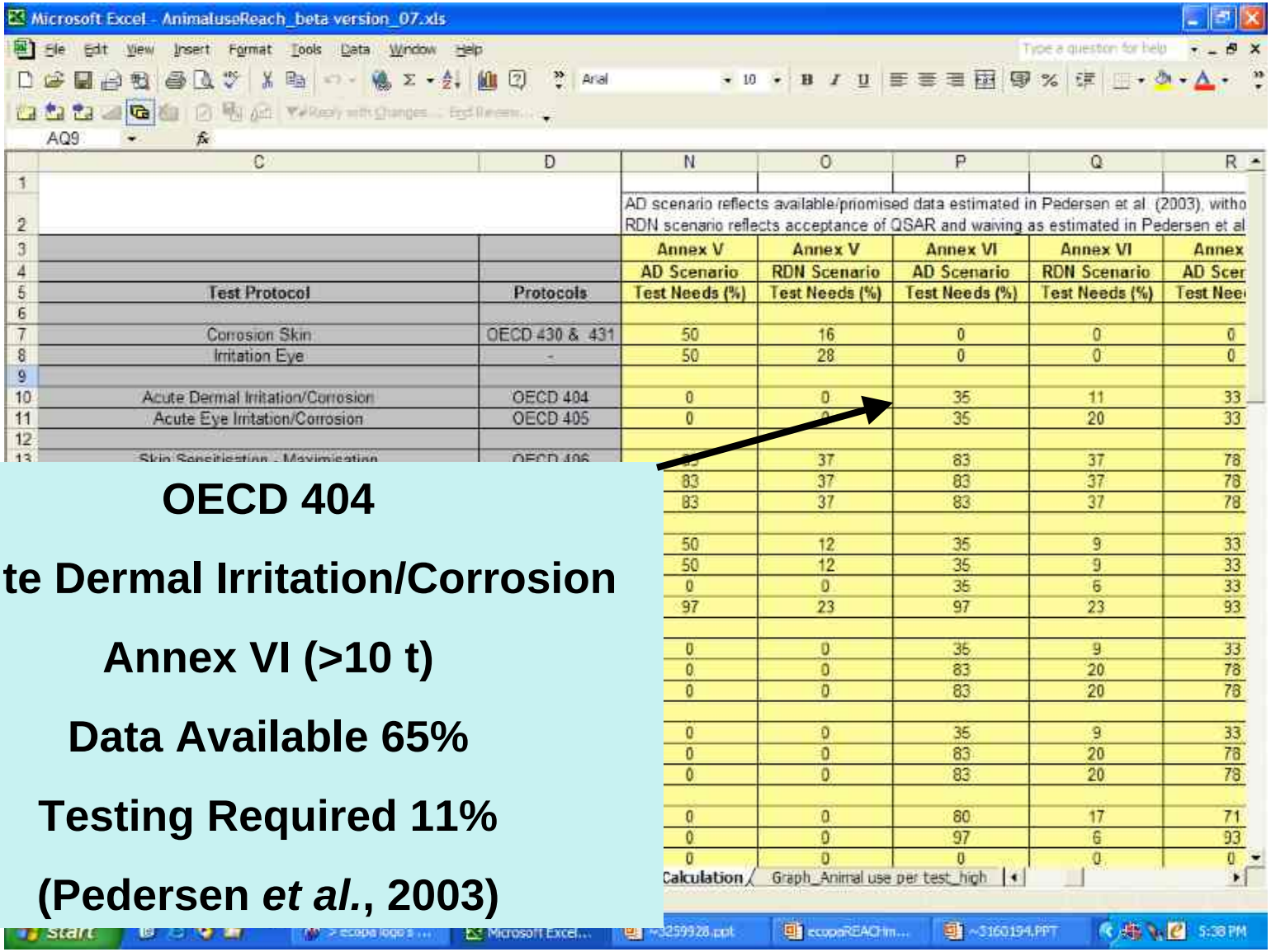


OECD 404

Acute Dermal Irritation/Corrosion:

1 – 3 animals

Data Availability/Actual Testing Need



OECD 404

Acute Dermal Irritation/Corrosion

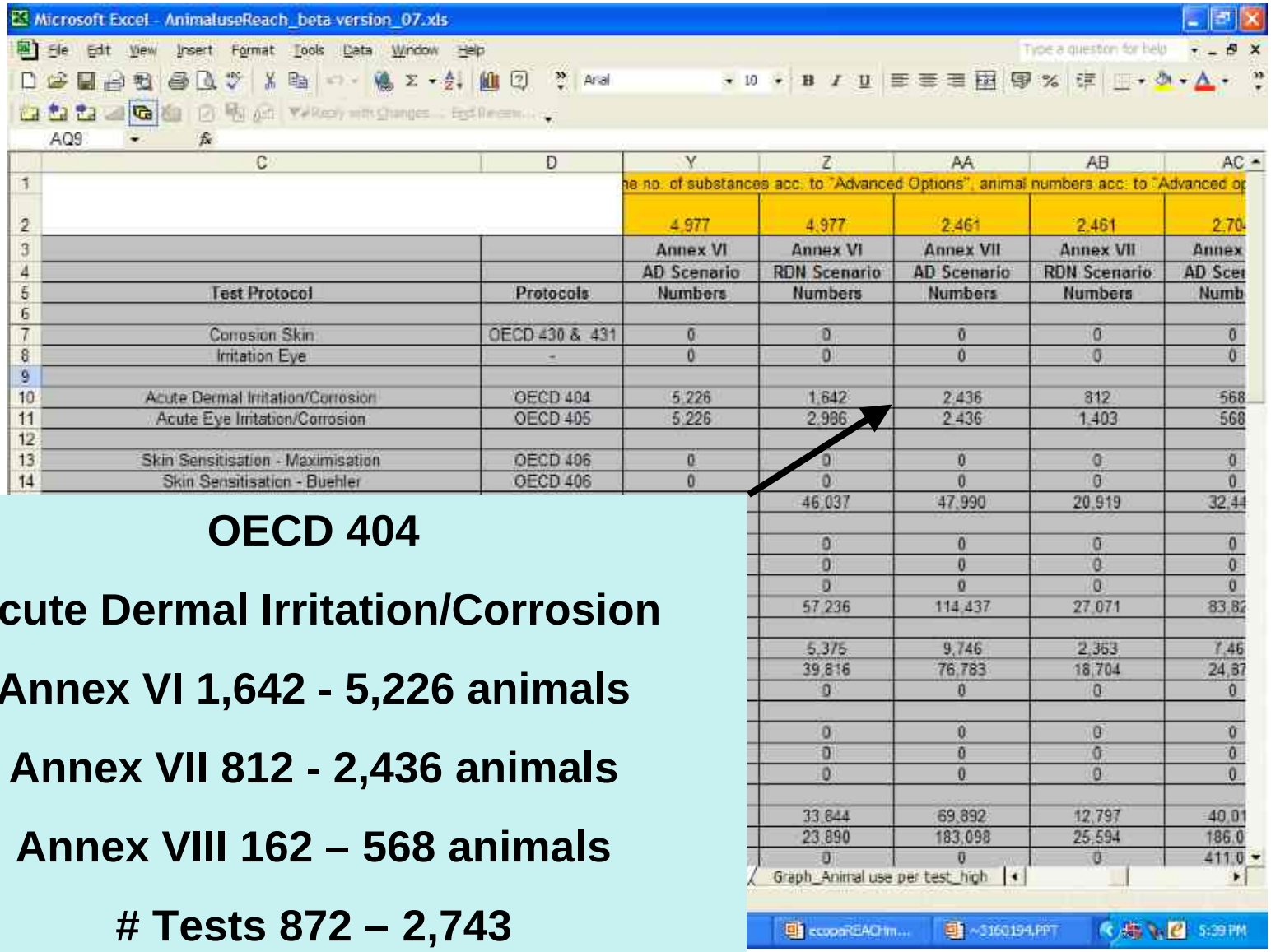
Annex VI (>10 t)

Data Available 65%

Testing Required 11%

(Pedersen *et al.*, 2003)

Projected Animal Use



	C	D	Y	Z	AA	AB	AC
1			he no. of substances acc. to "Advanced Options", animal numbers acc. to "Advanced op				
2			4,977	4,977	2,461	2,461	2,704
3			Annex VI	Annex VI	Annex VII	Annex VII	Annex
4			AD Scenario	RDN Scenario	AD Scenario	RDN Scenario	AD Scer
5	Test Protocol	Protocols	Numbers	Numbers	Numbers	Numbers	Numb
6							
7	Corrosion Skin	OECD 430 & 431	0	0	0	0	0
8	Irritation Eye	-	0	0	0	0	0
9							
10	Acute Dermal Irritation/Corrosion	OECD 404	5,226	1,642	2,436	812	568
11	Acute Eye Irritation/Corrosion	OECD 405	5,226	2,986	2,436	1,403	568
12							
13	Skin Sensitisation - Maximisation	OECD 406	0	0	0	0	0
14	Skin Sensitisation - Buehler	OECD 406	0	0	0	0	0
				46,037	47,990	20,919	32,44
				0	0	0	0
				0	0	0	0
				0	0	0	0
				57,236	114,437	27,071	83,82
				5,375	9,746	2,363	7,46
				39,816	76,783	18,704	24,87
				0	0	0	0
				0	0	0	0
				0	0	0	0
				0	0	0	0
				33,844	69,892	12,797	40,01
				23,890	183,098	25,594	186,0
				0	0	0	411,0

OECD 404

Acute Dermal Irritation/Corrosion

Annex VI 1,642 - 5,226 animals

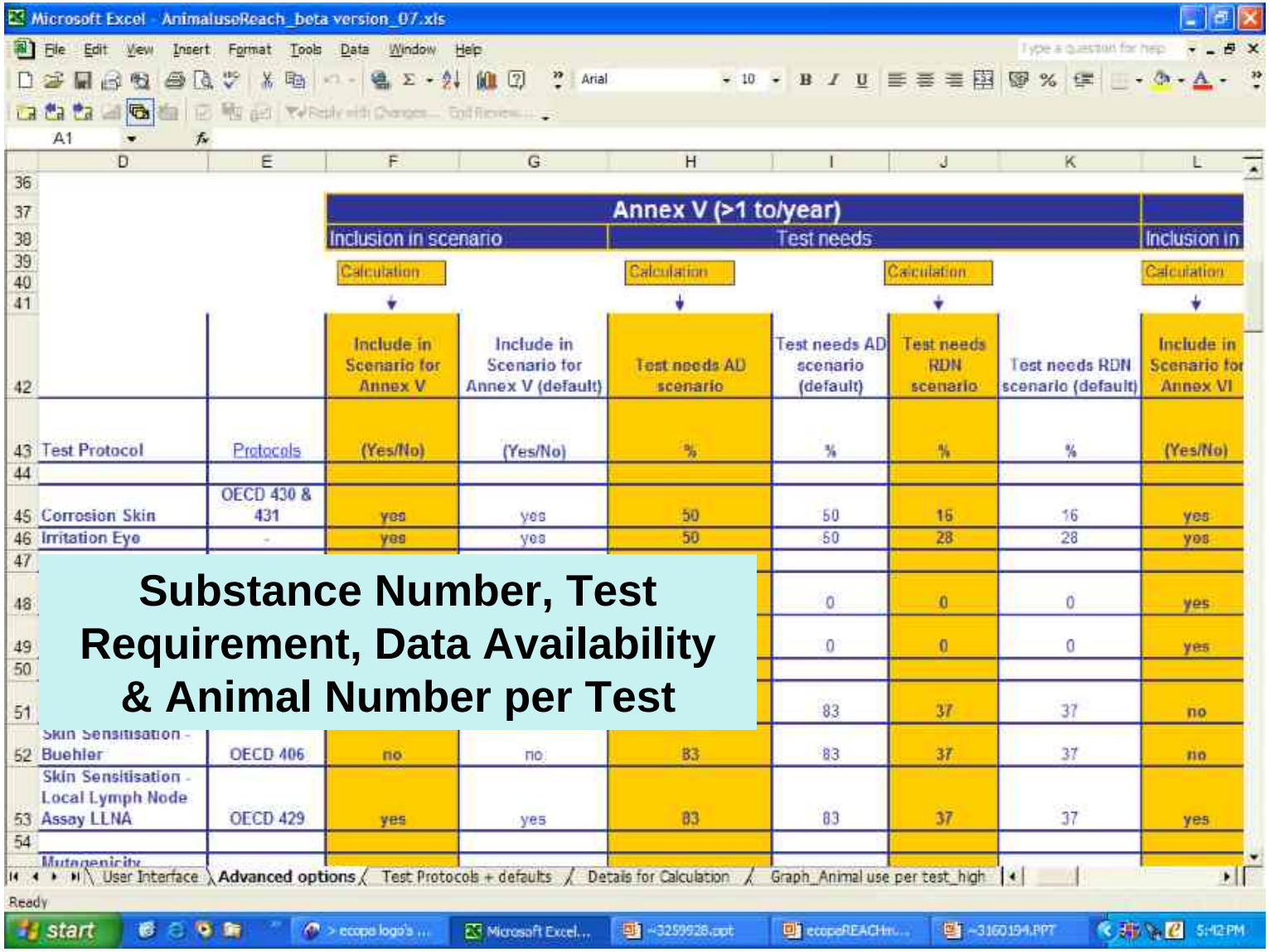
Annex VII 812 - 2,436 animals

Annex VIII 162 – 568 animals

 # Tests 872 – 2,743

Use of the Calculator

Modification of Assumptions



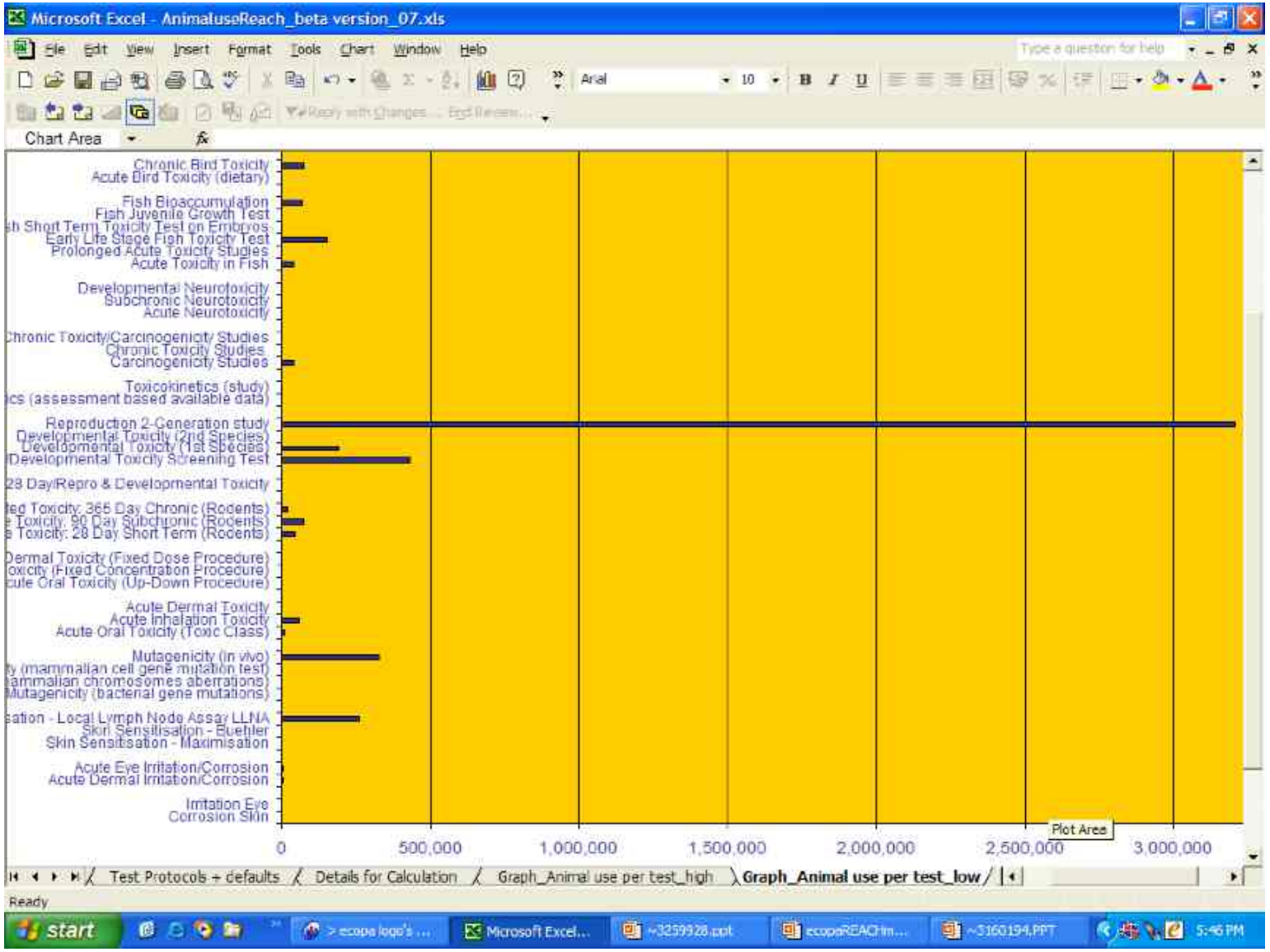
	D	E	F	G	H	I	J	K	L
36									
37			Annex V (>1 to/year)						
38			Inclusion in scenario		Test needs				Inclusion in
39			Calculation		Calculation		Calculation		Calculation
40			↓		↓		↓		↓
41									
42			Include in Scenario for Annex V	Include in Scenario for Annex V (default)	Test needs AD scenario	Test needs AD scenario (default)	Test needs RDN scenario	Test needs RDN scenario (default)	Include in Scenario for Annex VI
43	Test Protocol	Protocols	(Yes/No)	(Yes/No)	%	%	%	%	(Yes/No)
44									
45	Corrosion Skin	OECD 430 & 431	yes	yes	50	50	16	16	yes
46	Irritation Eye	-	yes	yes	50	50	28	28	yes
47									
48						0	0	0	yes
49						0	0	0	yes
50									
51						83	37	37	no
52	Skin Sensitisation - Buehler	OECD 406	no	no	83	83	37	37	no
53	Skin Sensitisation - Local Lymph Node Assay LLNA	OECD 429	yes	yes	83	83	37	37	yes
54									
	Mutagenicity								

User Interface | Advanced options | Test Protocols + defaults | Details for Calculation | Graph_Animal use per test_high

Ready

start | > ecopa logo's ... | Microsoft Excel... | ~3259928.ppt | ecopaREACHtu... | ~3160194.PPT | 5:42 PM

Graphical Output



1 - 10t/y (Annex V)

- ✓**Skin Corrosion/Irritation (assessment or *in vitro*)**
- ✓**Eye Irritation (assessment or *in vitro*)**
- ✓**Bacterial Gene Mutation**
- ✓**Skin Sensitization (LLNA)**
- ✓**Acute Oral Toxicity**

Source: Council Common Position December 13th 2005

10 - 100 t/y (Annex VI)

Those tests already mentioned for 1 - 10 t/y and:

- ✓***In vivo*** **Skin Irritation**
- ✓***In vivo*** **Eye Irritation**
- ✓***In vitro*** **Cytogenicity Test in Mammalian Cells**
- ✓***In vitro*** **Gene Mutation Test in Mammalian Cells**
- ✓**Acute Toxicity (2nd route)**
- ✓**28 day Repeat Dose Study**
- ✓**Reproductive & Developmental Screening Study**
- ✓**Acute Aquatic Toxicity-Fish**

Source: Council Common Position December 13th 2005

100 - 1000 t/y (Annex VII)

Those tests already mentioned for 10 - 100 t/y and:

- ✓**90 day Sub-Chronic Toxicity Study**
- ✓**Developmental Toxicity Study (one species)**
- ✓**Two-Generation Reproductive Study**
- ✓**Fish Early-life Stage, Embryo or Juvenile Growth Test**
- ✓**Bioconcentration in one Aquatic Species (Fish)**

Source: Council Common Position December 13th 2005

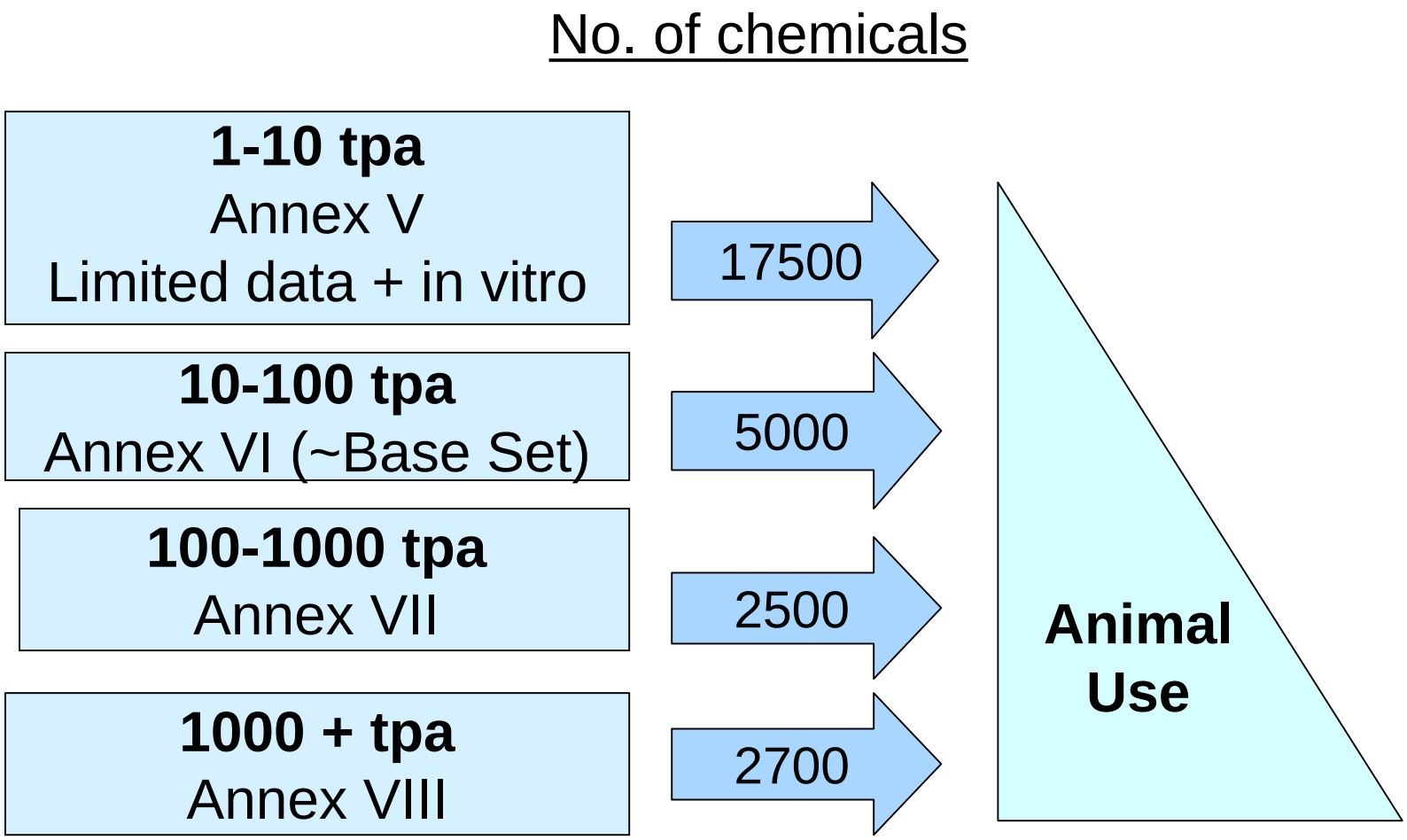
>1000 t/y (Annex VIII)

Those tests already mentioned for 100-1000t/y and if appropriate:

- ✓**Further Mutagenicity Test**
- ✓**Long-term Repeat Dose Study**
- ✓**Carcinogenicity Study**
- ✓**Long-term Reproductive Toxicity to Birds**

Source: Council Common Position December 13th 2005

Overall Data Requirements



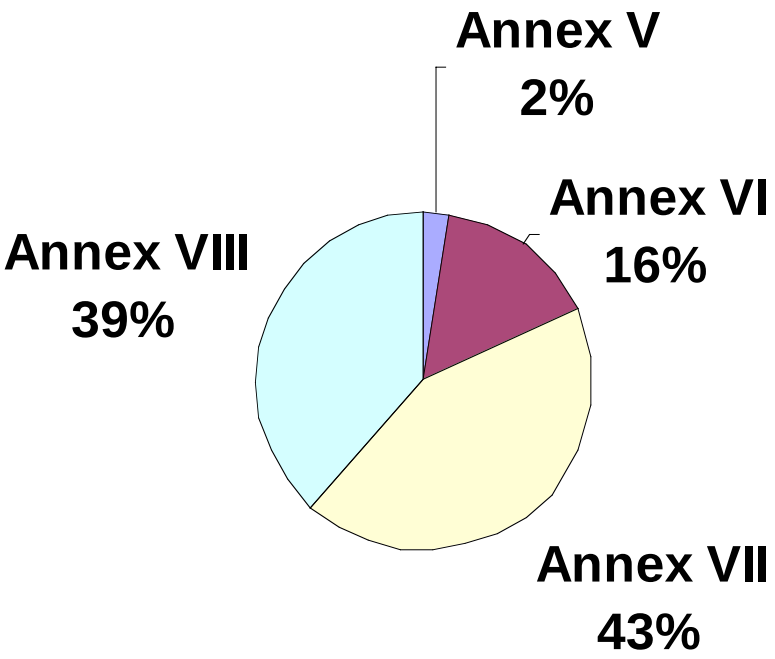
Key Input Assumptions

- **Calculator is highly dependent upon input assumptions**
- **Data availability and testing need is taken from ECB JRC (Pedersen *et al.*, 2003)**
- **Data availability is based on US EPA and ICCA HPV, IUCLID, VCI Voluntary Initiative etc.**
- **Two default scenarios with Standard tests: "*Available Data*" (AD) & "*Reduced Data Need*" (RDN)**
- **"*Available Data*" assumes that data is required in all cases if it does not exist already ("tick-box")**
- **"*Reduced Data Need*" assumes that testing is required for a subset of substances based on application of read-across, grouping, (Q)SAR, exposure-based waiving etc.**

Comparison of Scenarios

(Standard Tests Only)

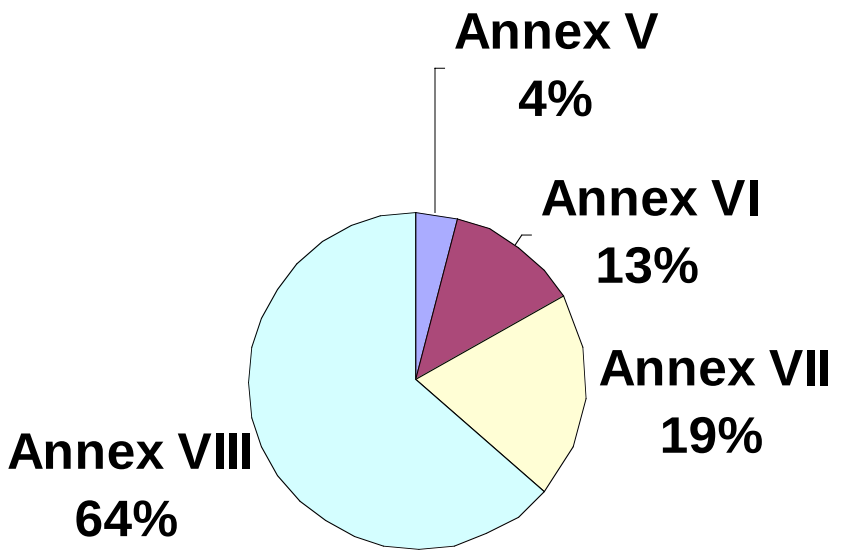
Available Data Scenario



16.21 Million Animals

7.00 Million Animals (- pups)

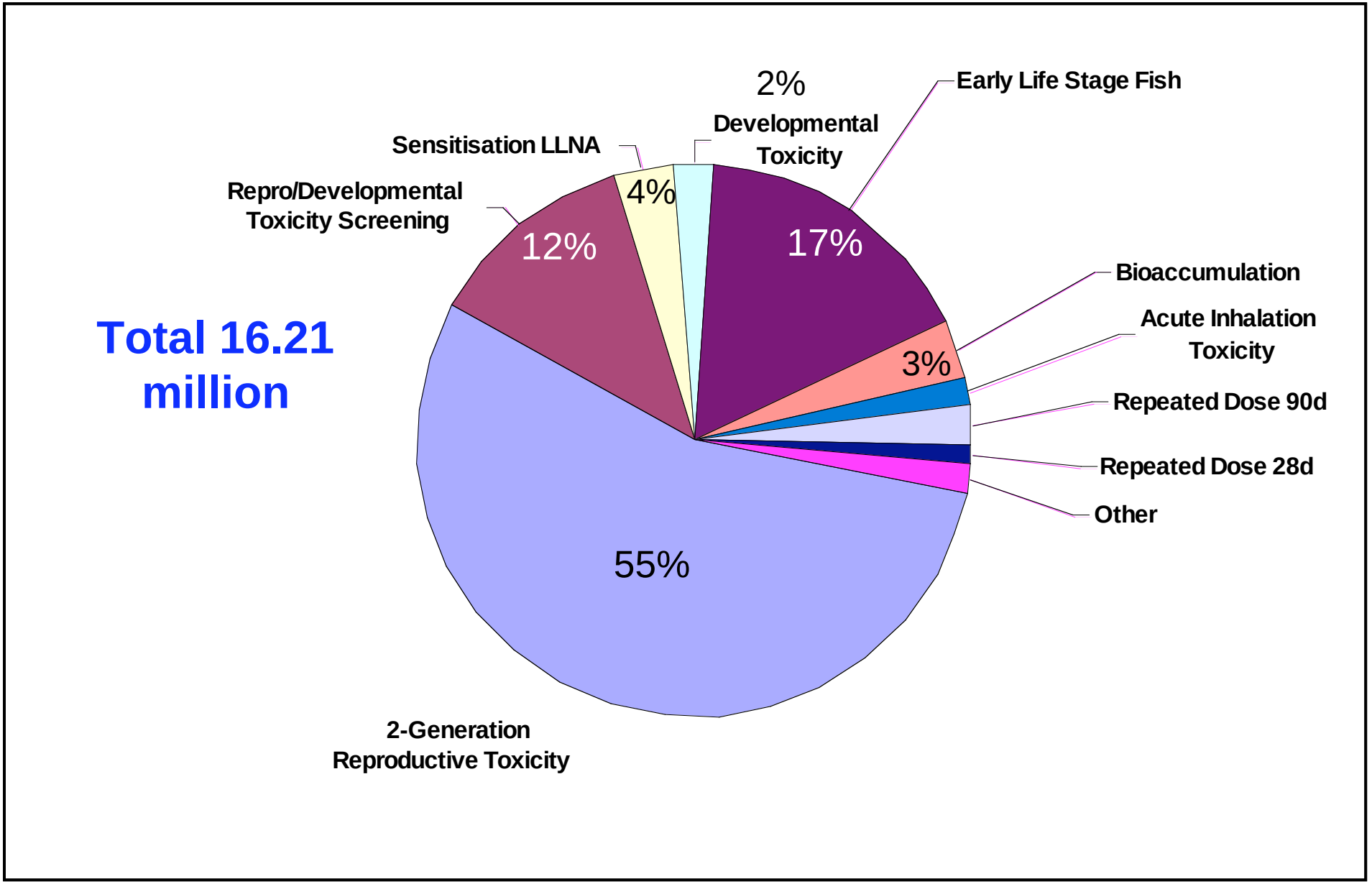
Reduced Data Need Scenario



4.52 Million Animals

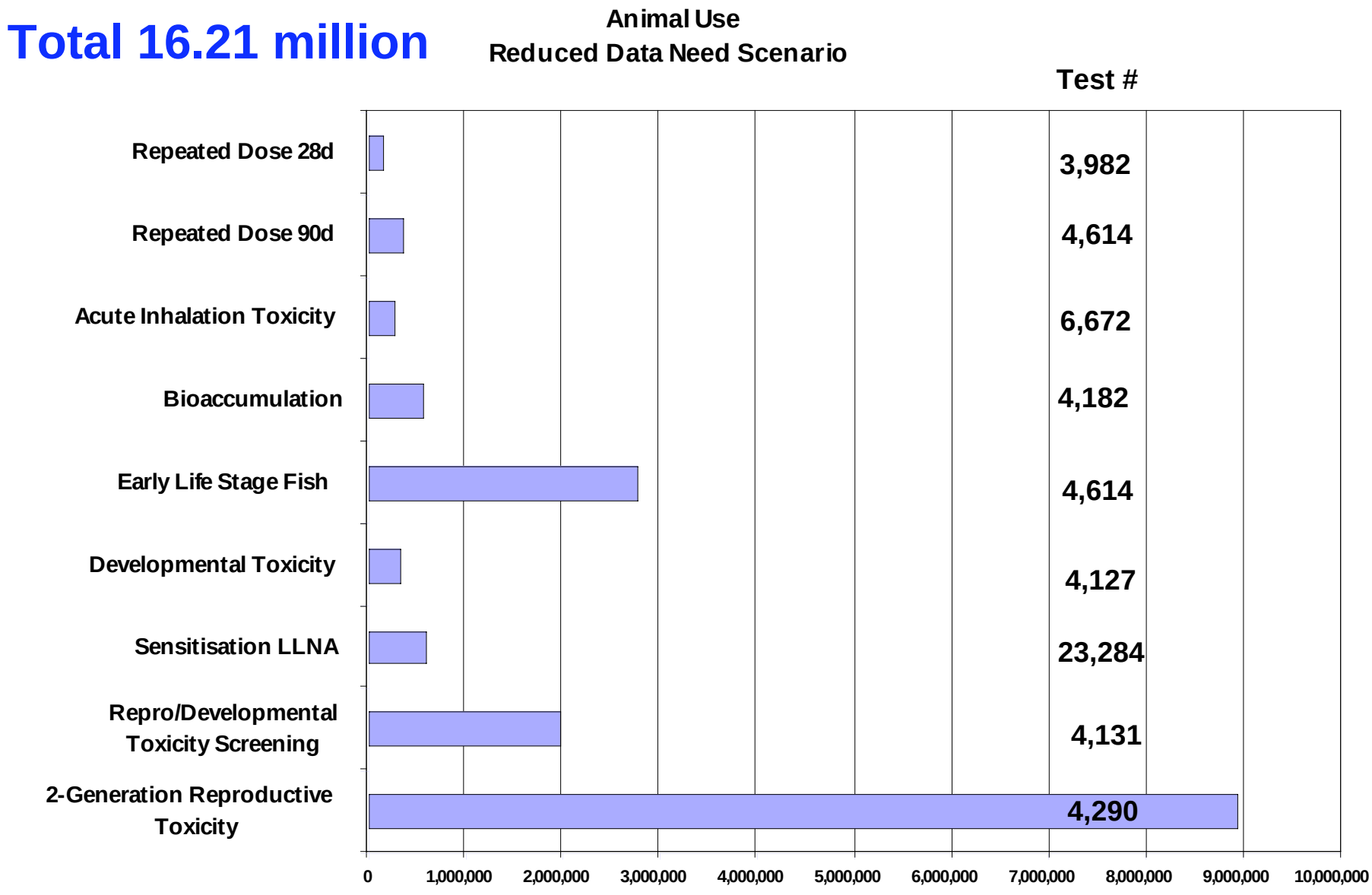
1.45 Million Animals (- pups)

Available Data Scenario



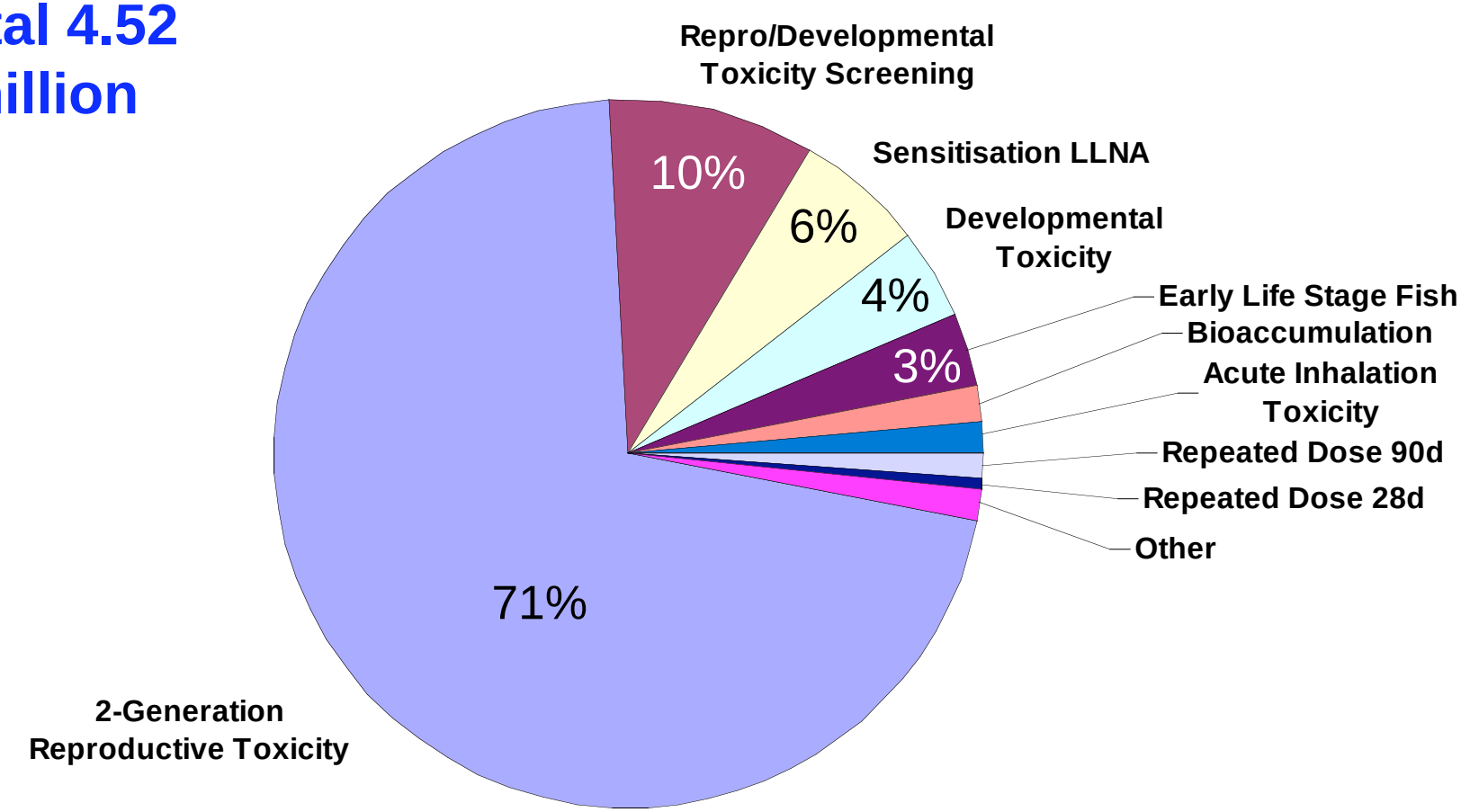
Available Data Scenario

Total 16.21 million



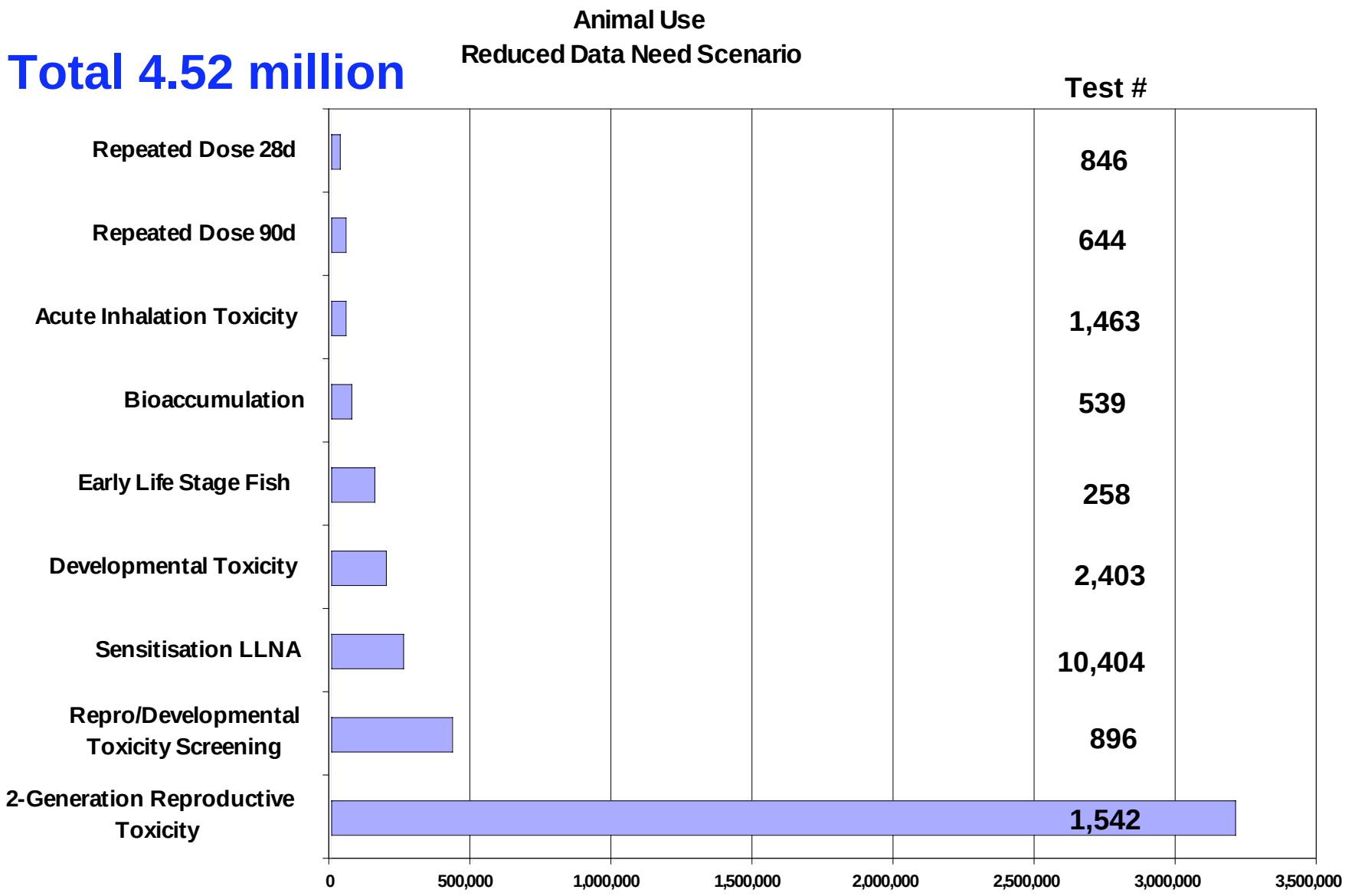
Reduced Data Need Scenario

Total 4.52 million



Reduced Data Need Scenario

Total 4.52 million



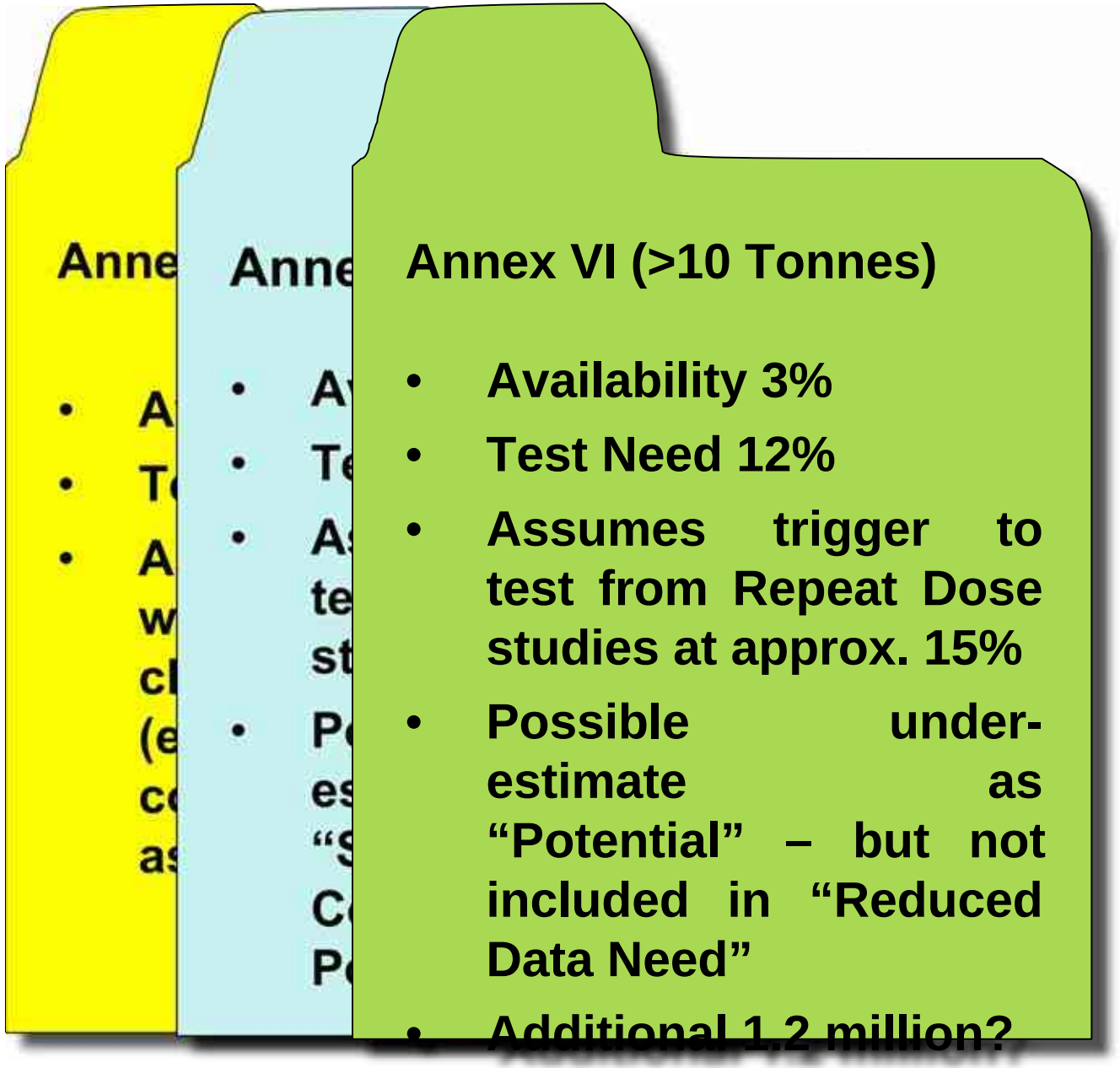
2-Generation Reproductive Toxicity

- **Data availability and test need from Pedersen *et al.* (2003)**
- **Largest number of animals for a single endpoint**
- **Calculator default includes pups so total animals per test are 2080 versus 320**
- **Regulatory "grey area"**
- **3.2 million animals or 71% in "*Reduced Data Need*" Scenario (1,542 tests)**
- **8.9 million or 55% in "*Available Data*" Scenario (4,290 tests)**

493,000

1,372,000

2-Generation Reproductive Toxicity

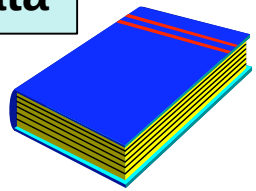


Reproductive Toxicity

- **Need to focus here (and other endpoints with high projected animal use) to refine predictions AND as priority for Intelligent Testing Strategies (ITS)**
- **ITS for Reproductive Toxicity proposed in RIP 3.3**
- **Tiered Approach in ILSI/HESI Agricultural Chemical Safety Assessment (ACSA)**
- **“ReProtect” aims to develop a suite of *in vitro* tests corresponding to the key components in the reproductive cycle (FP6 supported project)**

Testing Window

Mandatory Sharing of Vertebrate Data



>1-100t/y + substances intentionally released from articles

Pre-reg.

Registration

Evaluation

Testing Window (15.5 years) → 2024 Q2

Pre-reg.

>100-1000t/y +R50/53 1-100t/y

Registration

Evaluation

Testing Window (9.5 years)

Pre-reg.

>1000t/y + CMR 1&2 +R50/53 >100t/y

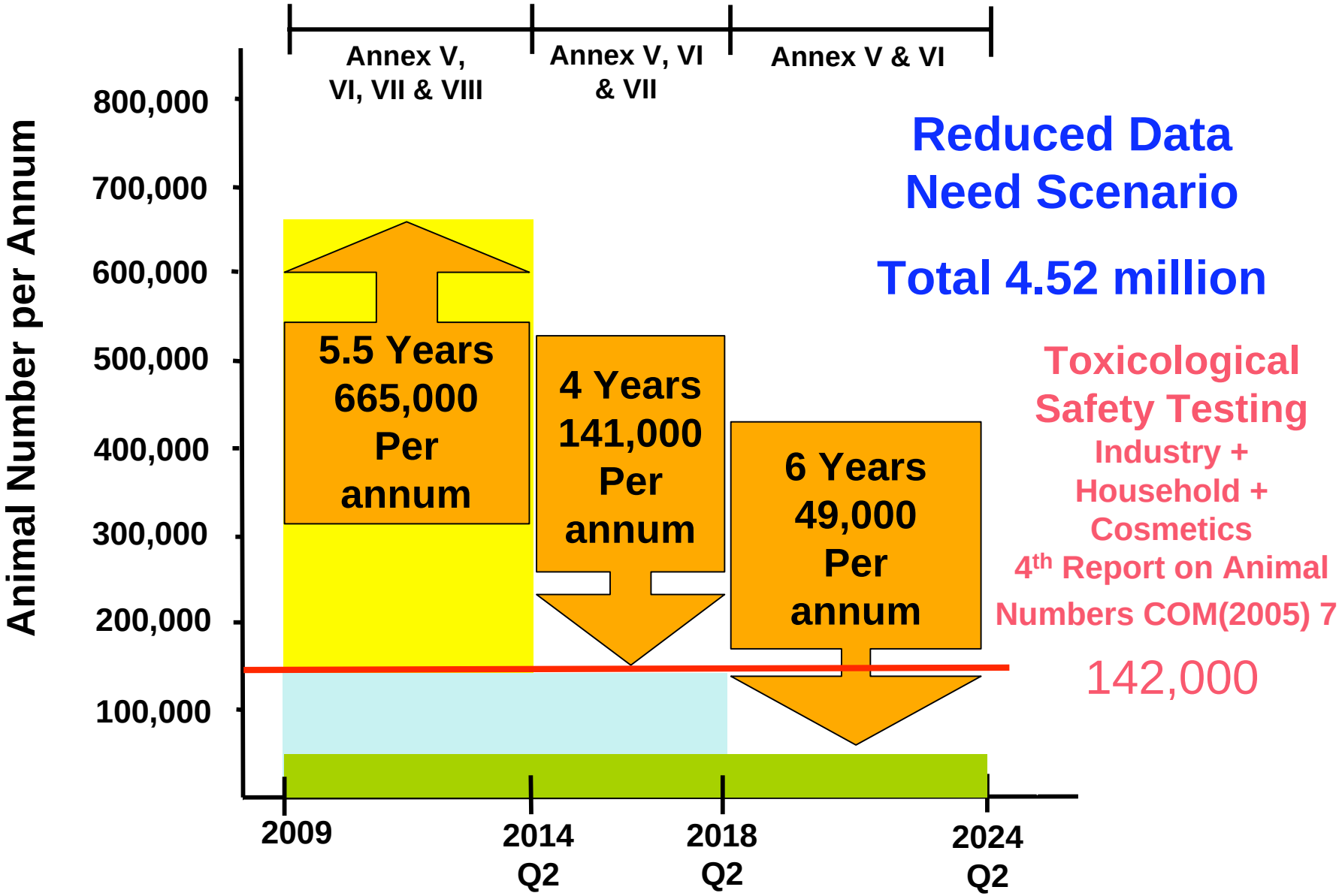
Reg.

Evaluation

Testing Window (5.5 years)

2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022

Animal Use Trend under REACH



Some Quick Observations

- **The numbers of laboratory animals required for REACH will dramatically increase animal use in the EU from 2010 until 2024 (especially <2014)**
- **Actual animal use will be highly dependent upon the interpretation of test needs by regulators (c.f. SPORT)**
- **"*Tick-box*" approaches will use many more animals**
- **There is a need to focus on endpoints with high projected animal use as priority for Intelligent Testing Strategies**

Summary of the Calculator

- There is no “right answer” as the results are highly dependent upon input assumptions
- The Calculator is an easily used tool that can be employed to quantify the impact of REACH in a transparent way
- The Calculator can provide a rational basis to highlight areas that will most benefit from efforts to reduce overall animal use (c.f. fish acute toxicity <1% versus reproductive toxicity circa 55-71%)
- The Calculator provides a clear rationale for ITS versus “box ticking” in terms of cost in animal lives
- The Calculator can also be used within companies and test consortia to quantify animal use associated with Registration of their chemical portfolios