Metrologically-related out-of-specification test results

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Investigating OOS test results of chemical composition based on metrological concepts

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The Barr court case 1993

In pharmaceutical industry, out-of-specification (OOS) test results are results that (after rounding off) fall outside the specifications or established acceptance criteria.

Barr Laboratories (a pharmaceutical company) was sued by US government regarding a set of issues influencing the product quality, including the way the company dealt with OOS results.

The judge Wolin's ruling (the Barr Decision): following an OOS result, an investigation must be initiated before any retesting can be done.

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FDA Guidance 2006

Guidance for Industry. Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

Identifying OOS results – Phase I: laboratory investigation
- responsibility of analyst (a control failure is not OOS),
- responsibility of laboratory supervisor.

Investigating OOS results – Phase II: full-scale investigation
- review of production (process review),
- additional lab testing (use a pre-defined procedure),
- reporting testing results (identify root cause).

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Metrological approach to OOS results

Investigation of OOS test results based on the metrological concepts should include :

1) assessment of validation data of the analytical method;

2) evaluation of the measurement uncertainty;

3) assessment of the metrological traceability chains;

4) assessment of consumer's and producer's risks.

I.Kuselman, F.Pennecchi, C.Burns, A.Fagjelj and P.Zorzi *Accreditation and Quality Assurance* 2010, 15:283-288

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Example 1. Total suspended particles (TSP)

INPL has tested amounts of TSP in air of 3 industrial zones/ quarries in Israel 2009. Four points in surrounding of every quarry were monitored 4-5 times per month, when the quarries worked.

Sampling (24 h) was performed by EPA method IO-2.1. A test result c_{test} was a ratio of the mass of filtered TSP to the sampled volume. The Israeli regulatory limit was 0.2 mg/m^3.

Total 220 test results (7 OOS) for the 1st quarry, 176 (11 OOS) for the 2nd, and 100 (2 OOS) for the 3rd quarry were obtained. Standard measurement uncertainty $u(c_{test})$ = 7% rel.

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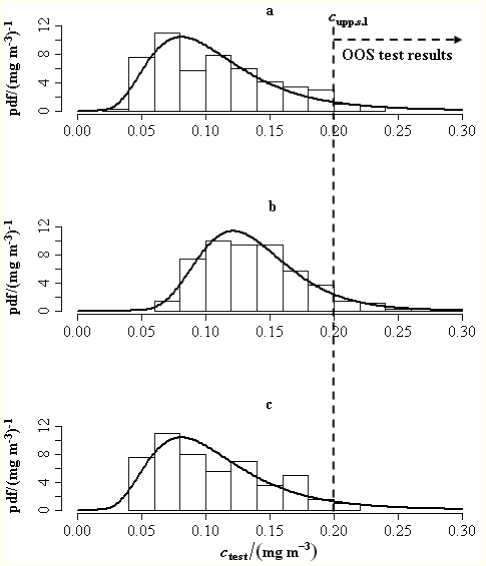
Histograms & pdf of lognormal distributions



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Deviations of OOS test results from $c_{u.s.l}$

Quarry	OOS test results		D_{OOS}	$U(c_{test})$		Metrologically-related?
	i	c_{test}		P= 0.95	P= 0.99	
1	1	0.210	0.010	0.029	0.044	maybe
	2	0.210	0.010	0.029	0.044	maybe
	3	0.204	0.004	0.029	0.043	maybe
	4	0.231	0.031	0.032	0.049	maybe
	5	0.210	0.010	0.029	0.044	maybe
	6	0.224	0.024	0.031	0.047	maybe
	7	0.223	0.023	0.031	0.047	maybe
2	1	0.223	0.023	0.031	0.047	maybe
	2	0.288	0.088	0.040	0.060	no ←
	3	0.211	0.011	0.030	0.044	maybe
	4	0.204	0.004	0.029	0.043	maybe
	5	0.255	0.055	0.036	0.054	no ←
	6	0.215	0.015	0.030	0.045	maybe
	7	0.211	0.011	0.030	0.044	maybe
	8	0.216	0.016	0.030	0.045	maybe
	9	0.226	0.026	0.032	0.047	maybe
	10	0.225	0.025	0.032	0.047	maybe
	11	0.232	0.032	0.032	0.049	maybe
3	1	0.206	0.006	0.029	0.043	maybe
	2	0.218	0.018	0.031	0.046	maybe

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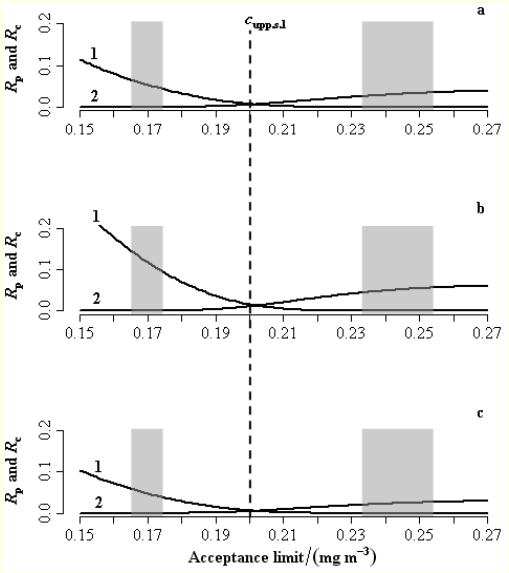
Risks of the producers R_p and inhabitants R_c



I.Kuselman, S.Shpitzer, F.Pennecchi, C.Burns *Air Quality, Atmosphere and Health* 2010 DOI 10.1007/s 11869-010-0103-6

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Example 2. Pesticide residues in tomatoes

Characterization of food quality is based on the food chemical analysis/testing and comparison of the test results c_{test} with specification or other statutory limits.

In particular, there exist national legal maximum residue limits *MRL* of pesticide mass concentrations in tomatoes (mg/kg by the European Guidance SANCO 2009) or related tolerances (parts per million by US EPA 2009).

OOS test results are results which do not comply with the national *MRL*.

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Database

As a case study, data were investigated obtained in Israel in 2009 by the Laboratory for Pesticide Residue Analysis in framework of the Pesticide Monitoring Program of the Plant Protection and Inspection Services (PPIS), Ministry of Agriculture and Rural Development.

169 samples of tomatoes were analyzed using GC methods with flame photometric and halogen selective detectors, as well as with a mass spectrometer. LC/tandem mass spectrometry was also applied.

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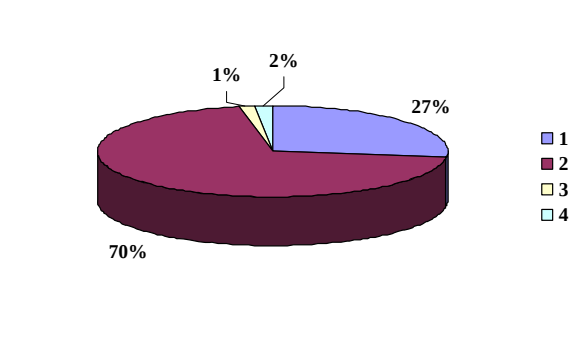
Analytes, their occurrence and MRL values

Analyte	Occurrence (%)	c_{test} (mg/kg)	*MRL* (mg/kg)	Analyte	Occurrence (%)	c_{test} (mg/kg)	*MRL* (mg/kg)
Azoxystrobin	2.4	0.04-0.11	0.5	Folpet	0.6	0.20	0.5
Bifenazate	3.0	0.02-0.04	0.05	Iprodione	3.0	0.16-0.76	5
Boscalid	3.6	0.01-0.10	0.2	Iprovalicarb	0.6	0.04	0.05
Carbendazim	0.6	0.41	0.1	Lufenuron	0.6	0.02	0.05
Carbosulfan	0.6	0.01	0.1	Mepanipyrim	0.6	0.11	0.1
Chlorothalonil	18.3	0.01-1.33	5	Metalaxyl	3.0	0.01-0.09	0.5
Chlorpyrifos	1.8	0.01-0.39	0.5	Metominostrobin	1.2	0.01-0.14	0.2
Clofentezine	0.6	0.13	1	Myclobutanil	1.2	0.06-0.08	0.3
Cymoxanil	0.6	0.02	0.05	Novaluron	0.6	0.02	0.2
Cypermethrin	0.6	0.08	0.5	Penconazole	3.0	0.03-0.11	0.2
Cyprodinil	2.4	0.02-0.31	0.5	Propargite	0.6	0.10	2
Diafenthiuron	0.6	0.05	0.05	Pyrimethanil	0.6	0.03	0.05
Diazinon	0.6	0.03	0.5	Spiromesifen	3.6	0.01-0.28	1
Diethofencarb	1.2	0.01-0.04	0.1	Tebuconazole	1.8	0.03-0.11	0.2
Difenoconazole	0.6	0.09	0.1	Tebufenpyrad	0.6	0.03	0.05
Dimethoate	0.6	0.01	1	Tetradifon	1.2	0.01-0.07	1
Endosulfan	0.6	0.08	0.5	Thiamethoxam	0.6	0.03	0.02
Fenazaquin	1.2	0.02-0.33	0.1	Triadimenol	5.9	0.01-0.19	0.5
Fenhexamid	0.6	0.03	0.5	Trifloxystrobin	2.4	0.03-0.75	0.2
Fludioxonil	1.8	0.01-0.11	0.3				

Summary of the data



1 corresponds to % of c_{test}= 0 (not detected); 2 – % of 0 < c_{test} ≤ *MRL* when analytes were detected, but their concentrations did not exceed *MRL*; 3 – % of OOS test results *MRL*< c_{test} ≤ 2*MRL* which did not violate the legal limits by SANCO 2009; and 4 – % of violated OOS test results c_{test} > 2*MRL*.

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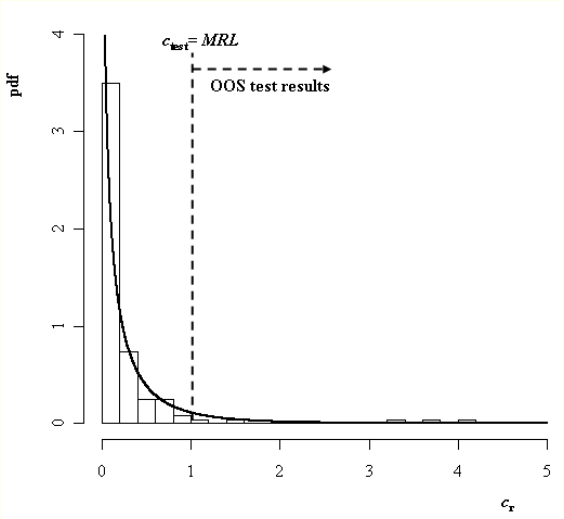
Histogram of c_r values and the Weibull pdf



The histogram was plotted for c_r > 0, i.e., for 123 samples in which one or more pesticide residues were detected, identified and quantified.

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Comparison of c_r with $U(c_{test})$

OOS test results			Metrologically-related? *		
Analyte	c_{test} (mg/kg)	c_r	$P = 0.95$	$P = 0.99$	
Carbendazim	0.41	4.1	No	No	←
Fenazaquin	0.33	3.3	No	Maybe	←
Mepanipyrim	0.11	1.1	Maybe	Maybe	
Thiamethoxam	0.03	1.5	Maybe	Maybe	
Trifloxystrobin	0.75	3.8	No	Maybe	←

* "No" is for P = 0.95 when $c_r > 2$, and for P = 0.99 when $c_r > 4$.

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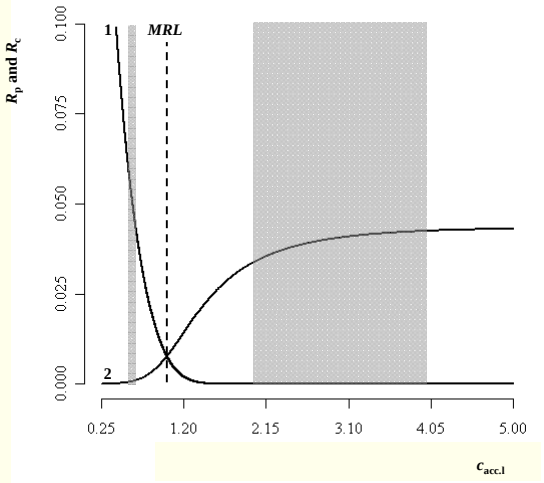
Producer's and consumer's risk values



I.Kuselman, P.Goldshlag, F.Pennecchi, C.Burns *Accreditation and Quality Assurance* 2011 DOI 10.1007/s 00769-011-0780-3

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Example 3. Retest period or shelf life by ICH

Guidelines ICH Q1E allows to establish a retest period or shelf life of a drug product using regression analysis of stability data (e.g. assay results vs. time) accumulated during long-term storage of the product.

For a measured property of the product known to decrease (or increase) with time, the lower (or upper) one-sided 0.95 confidence limit for the mean should be compared to the acceptance criterion. The retest period (shelf life) is estimated as the earliest time at which the confidence limit intersects the criterion.

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OOS test results in stability study

The acceptance criterion may be formulated as a requirement to an analyte concentration in a product not to exceed the upper specification limit $c_{u.s.l}$, or not to be less than the lower limit $c_{l.s.l}$. However, true values c_{true} are unknown and test results c_{test} are affected by the measurement uncertainty.

Therefore, OOS test results $c_{test} > c_{u.s.l}$ or $c_{test} < c_{l.s.l}$ in stability study can indicate an actual change (degradation) of the product or be metrologically-related with probability P, i.e., be caused by the measurement problems, though the product still meets the quality requirements at the time of testing.

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Examples 3a and 3b

The test results of sodium chloride injection in plastic containers and epinephrine injection in ampoules, stored over 10-20 years in the R&QC Lab, IDF, were discussed.

During storage of NaCl injection an amount of water permeates from inside the container into the over-wrap space due to evaporation through the plastic. Therefore, c_{test} values were compared with $c_{u.s.l}$ = 105.0%.

L-adrenaline in the solution is subject of degradation during storage, caused by oxidation, sulfonation and racemization Therefore, c_{test} were compared here with $c_{l.s.l}$ = 90.0 %.

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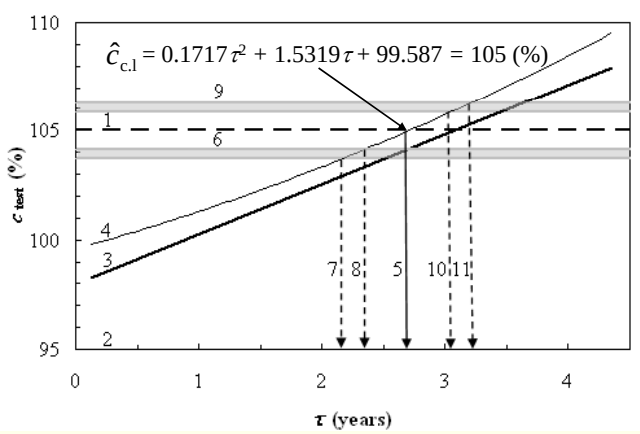
Specification limits and shelf life of the sodium chloride injection



Gray bars are the corridors of the c_{test} at P = 0.95-0.99. The product shelf life is $\tau_0 = \left[-b_1 \pm \sqrt{b_1^2 - 4b_2(b_0 - \hat{c}_{c.l})}\right]/2b_2$.

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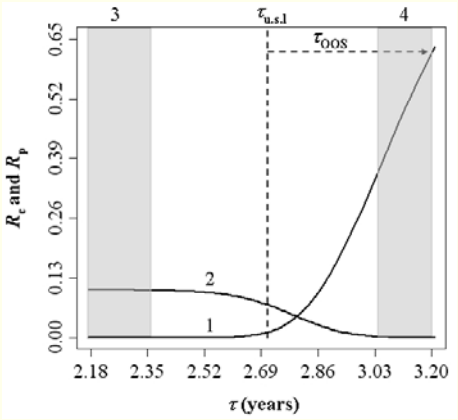
Risks of consumer R_c and producer R_p of sodium chloride injection vs. τ



R_c and R_p values were calculated with respect to an $c_{acc.l}$ equal, for each τ, to the relevant one-sided upper 0.95 confidence limit to the regression line.

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Conclusions

1. Any OOS test result can indicate an analyte concentration in the product/environment violating the specification/legal limit, or be caused by measurement/metrological problems, i.e., be metrologically-related.

2. A metrological approach used for investigating OOS test results allows detection of those of them which can be considered as metrologically-related.

3. Global risks of producer and consumer caused by metrologically-related OOS test results (probabilities of false decisions on quality of a product) can be evaluated taking into account the measurement uncertainties.

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