

## Appendix D

### D. CASE STUDY II: RESULTS FOR THE EFFECT OF INCOMING DATA

Additional results for Case Study II are presented in Appendix D, which have been referred to in Chapter 7. The cumulative frequency plots for the predicted total yield at different levels of knowledge are shown in Figure D1. Knowledge level 6 shows evidence that it provides the best prediction to the plant data since the distribution clearly encompasses the data point value (solid vertical line). Figure D2 shows the corresponding plots for the predicted key impurity endpoint content and that knowledge levels 3, 4, 5, and 6 exhibit the least uncertainty for this criterion. The main Sensitivity Analysis results for the different knowledge levels are shown in Table D1. The scatter plots for knowledge level 0 data, Figure D3, verify that the scatter of the key impurity reaction rate constant,  $k_2$ , and the key impurity ‘solute loss’ parameter,  $\zeta_{actC}$ , with the endpoint key impurity content, are comparable (SRC of 0.78 and 0.77, Table D1). The relative uncertainty for the post-reactor key impurity composition and the endpoint content, shown in the cumulative frequency plots, Figure D4, indicate that a large proportion of the uncertainty accumulated in the endpoint criterion appears to be already present after Stage 1 (corresponding to a Stage 1 sub-sequence contribution of 0.62 compared to Stage 2-15 contribution of 0.38).

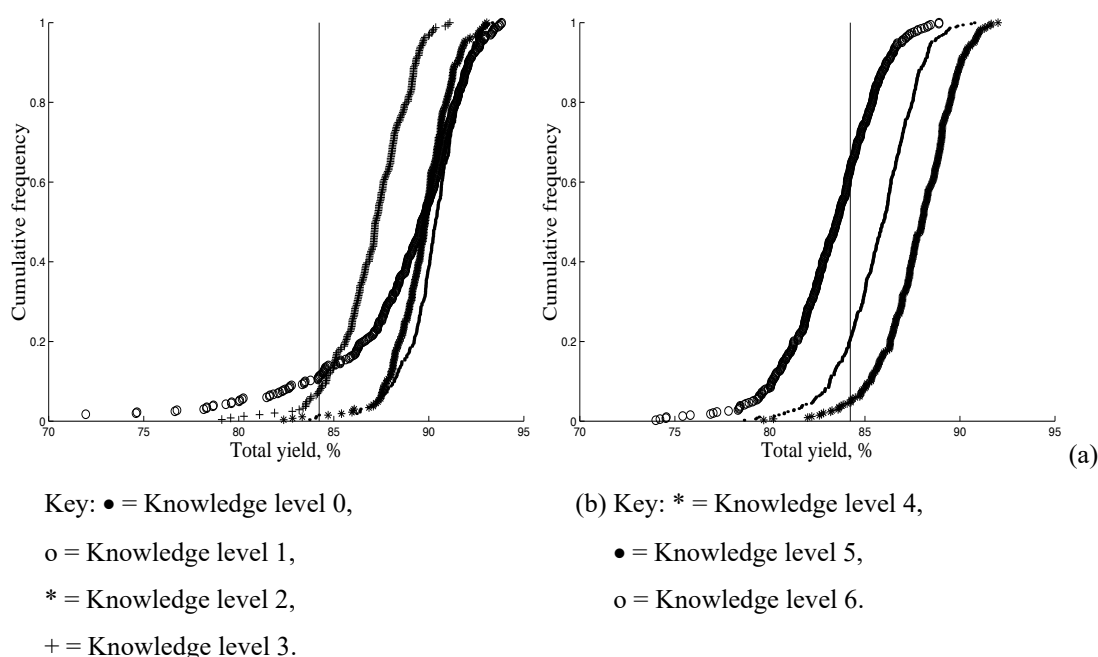


Figure D1. Cumulative frequency plots of total yield prediction under uncertainty, Case Study II.

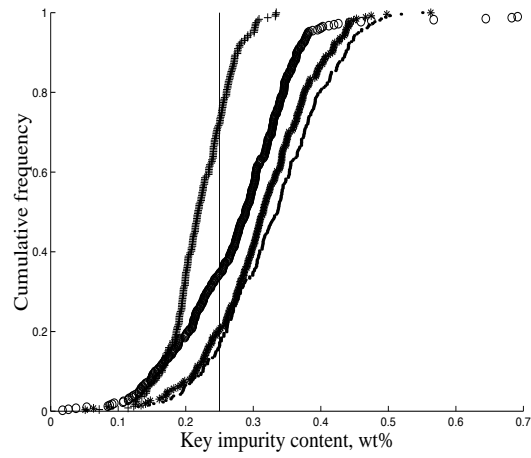


Figure D2. Cumulative frequency plots of key impurity content prediction, Case Study II.  
 Key: • = Knowledge level 0, o = Knowledge level 1, \* = Knowledge level 2,  
 + = Knowledge level 3, 4, 5, and 6.

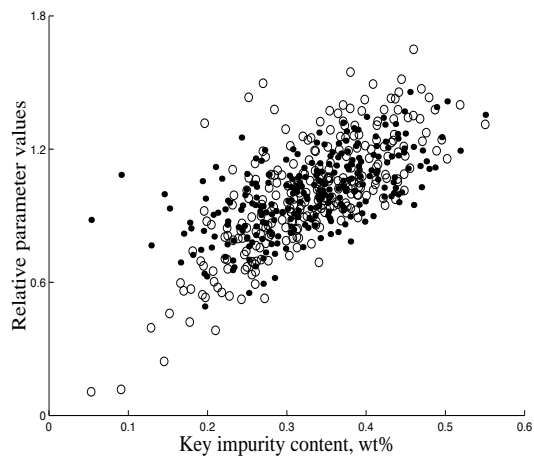


Figure D3. Scatter plots of the key parameters with the endpoint key impurity content, Case Study II.  
 Key: • = Key impurity reaction rate constant,  $k_2$ , o = Key impurity 'solute loss' parameter,  $\zeta_{actC}$ .

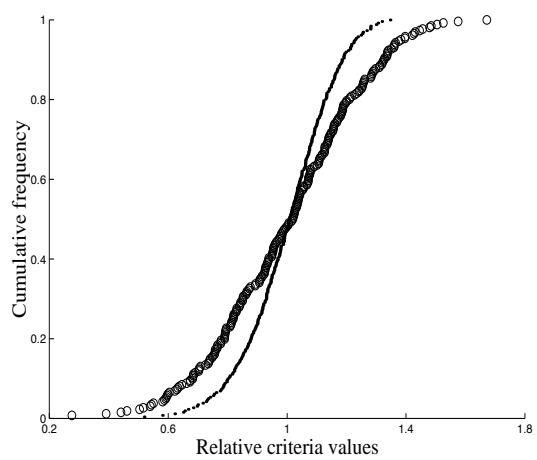


Figure D4. Cumulative frequency plots of inter-stage key impurity composition under uncertainty, Case Study II.

Key: ● = Post-reaction key impurity composition, wt%, ○ = Endpoint key impurity content, wt%.

Table D1. Main SRC Sensitivity Analysis results for levels of knowledge incorporation, Case Study II.

Knowledge level	Endpoint criteria					
	Total yield		Key impurity content		Secondary impurity content	
0	R <sup>2</sup>	0.97	R <sup>2</sup>	0.98	R <sup>2</sup>	0.99
	k <sub>g</sub>	0.82	ζ <sub>actC</sub>	0.78	ζ <sub>actE</sub>	0.96
	k <sub>1</sub>	0.32	k <sub>2</sub>	0.77	k <sub>3</sub>	0.32
	u <sub>1</sub>	-0.17 to -0.20	η <sub>wash</sub>	-0.21	η <sub>wash</sub>	-0.19
	u <sub>2</sub>	-0.15 to -0.18				
1	R <sup>2</sup>	0.80	R <sup>2</sup>	0.96	R <sup>2</sup>	0.97
	k <sub>1</sub>	0.80	ζ <sub>actC</sub>	0.61	ζ <sub>actE</sub>	0.76
	k <sub>g</sub>	0.40	k <sub>2</sub>	0.58	k <sub>3</sub>	0.60
	u <sub>1</sub>	-0.12 to -0.13	η <sub>wash</sub>	-0.18	η <sub>wash</sub>	-0.10
	u <sub>2</sub>	-0.10 to -0.12				
2	R <sup>2</sup>	0.97	R <sup>2</sup>	0.99	R <sup>2</sup>	0.97
	k <sub>g</sub>	0.79	ζ <sub>actC</sub>	0.72	k <sub>3</sub>	0.73
	k <sub>1</sub>	0.30	k <sub>2</sub>	0.66	ζ <sub>actE</sub>	0.67
	u <sub>1</sub>	-0.15 to -0.22	η <sub>wash</sub>	-0.20	η <sub>wash</sub>	-0.14
	u <sub>2</sub>	-0.16 to -0.21				
3	R <sup>2</sup>	0.97	R <sup>2</sup>	0.99	R <sup>2</sup>	0.99
	k <sub>g</sub>	0.67	k <sub>2</sub>	0.89	k <sub>3</sub>	0.89
	k <sub>1</sub>	0.58	ζ <sub>actC</sub>	0.54	ζ <sub>actE</sub>	0.44
	t''	-0.29	t''	-0.27	η <sub>wash</sub>	-0.15
	u <sub>2</sub>	-0.13 to -0.21	η <sub>wash</sub>	-0.25		
	γ <sub>1</sub>	-0.16	γ <sub>1</sub>	-0.14		
	γ <sub>2</sub>	-0.16	γ <sub>2</sub>	-0.13		
	u <sub>1</sub>	-0.13 to -0.14				
4	R <sup>2</sup>	0.97	R <sup>2</sup>	0.98	R <sup>2</sup>	0.99
	k <sub>g</sub>	0.60	k <sub>2</sub>	0.89	k <sub>3</sub>	0.87
	k <sub>1</sub>	0.58	ζ <sub>actC</sub>	0.55	ζ <sub>actE</sub>	0.45
	t''	-0.30	t''	-0.26	η <sub>wash</sub>	-0.15
	u <sub>1</sub>	-0.14 to -0.17	η <sub>wash</sub>	-0.25		
	γ <sub>1</sub>	-0.15	γ <sub>1</sub>	-0.14		
	γ <sub>2</sub>	-0.15	γ <sub>2</sub>	-0.12		
5	R <sup>2</sup>	0.97	R <sup>2</sup>	0.99	R <sup>2</sup>	0.99
	k <sub>g</sub>	0.64	k <sub>2</sub>	0.75	k <sub>3</sub>	0.88
	k <sub>1</sub>	0.47	ζ <sub>actC</sub>	0.63	ζ <sub>actE</sub>	0.44
	σ <sub>sl</sub>	-0.23 to 0.44	t''	-0.27	η <sub>wash</sub>	-0.14
	t''	-0.29	η <sub>wash</sub>	-0.20		
	γ <sub>1</sub>	-0.17	γ <sub>1</sub>	-0.15		
	γ <sub>2</sub>	-0.15	γ <sub>2</sub>	-0.12		
6	R <sup>2</sup>	0.97	R <sup>2</sup>	0.99	R <sup>2</sup>	0.99
	k <sub>g</sub>	0.77	k <sub>2</sub>	0.75	k <sub>3</sub>	0.88
	k <sub>1</sub>	0.38	ζ <sub>actC</sub>	0.63	ζ <sub>actE</sub>	0.44
	σ <sub>sl</sub> *	-0.20 to 0.36	t''	-0.26	η <sub>wash</sub>	-0.13
	t''	-0.24	η <sub>wash</sub>	-0.19		
	γ <sub>1</sub>	-0.14	γ <sub>1</sub>	-0.15		
	γ <sub>2</sub>	-0.12	γ <sub>2</sub>	-0.12		