Department of Defense Comments on the Draft Toxicological Review of Urea, June 2010					
Comments submitted by: Chemical Material Risk Management Directorate		Organization: Department of Defense		Date Submitted: 2 July 2010	
*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.					
Comment No.	**Section**	**Page & Paragraph (enter "Global" if report section-wide)**	**Comment**	**Suggested Action, Revision and References (if necessary)**	**Category***
1	2. Chemical And Physical Information	Page 4: 1st Para	We have noticed some recent IRIS Toxicological Reviews have based the toxicity of a chemical on its metabolites, here we note that EPA chose not to examine the potential toxicity of urea's metabolites, ammonia and carbon monoxide for example.	The document should clearly state the rationale for determining whether to evaluate metabolites and degradation products in the Toxicological Review, and which ones are appropriate for analysis.	S
2	2. Chemical and Physical Information	Page 5, 2nd Para	Inhalation and dermal routes being the most probable occupational routes of exposure is inconsistent with first sentence of Section 3.1, which states that the primary route of exposure is oral.	Clarify statements so they do not provide inconsistent information.	E
3	3. Toxicokinetics	Page 7: 2nd Para	Unlike previous IRIS reviews of endogenously occurring chemicals where all data on the chemical was reviewed, EPA states for this chemical that *"This section will only present results from studies of exogenously administered urea."* It is not clear why EPA is discounting the stated *"majority of the literature"* that addresses endogenous urea.	The Toxicological Review should clearly state the decision criteria regarding the use of data on endogenous and exogenous forms of the chemical and its evaluation of the chemical's potential toxicity.	S
4	3.3. Metabolism 3.5. Physiolo-	Page 12, 1st Para	This section initially states that *"there is little evidence that endogenous urea is metabolized"*, but it does demonstrate that urea is readily hydrolyzed in the g.i. tract. The statement seems to be also in contradiction with the PBPK model in figure 3.2 (page 19), where (according to the	If bacterial hydrolysis is not considered metabolism please explain where EPA believes these transformations would be considered in the toxicokinetics (TK) of a chemical.	S

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	gically Based Toxicokinetic Models	Page 19	discussion in the text) Pool A is the urea of hepatic origin (hence inside the body) and the elimination from this pool includes that of bacterial hydrolysis. Does this mean that EPA does not consider chemical changes in the g.i. tract "metabolism"?		
5	4.1.2.1 Cohort Studies 4.7 Evaluation of Carcino-genicity 5.2.1 Choice of Principa Study ad Critical Effect – with Rationale and Justification	Pages 25, 2nd Para Page 75, 1st Para Page 80, 1st Para	We are pleased that EPA recognizes the limited significance of statistically significant increases in biomarkers when these are within *"normal physiologic range"*.	This continued practice will certainly contribute to the transparency of the documents in future reviews.	O
6	3.5 Physiolo-gically Based Toxicokinetic Models	Page 20, 1st Para	We believe the *"F"* in the second line needs a subscript, probably *"oa"*	Please correct as warranted.	E

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7	4.1.2.1 Cohort Studies	Page 26, 1st Para	This analysis appears to discount statistically significant changes in peak expiratory flow rate per minute (PEFR/min) in the absence of significant changes in forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) that are said to be the *"screening markers for obstructive or restrictive pulmonary effects."* While we do not object to this conclusion, we believe it is not consistent with at least one analysis in another recent IRIS document.	The quality control procedures for producing IRIS documents should ensure biomarkers and test results are given similar interpretations for every chemical analyzed within the same time frame. When substantial differences in interpretation are made due to changes in understanding of the results, these should be noted.	O
8	4.2.1.2 Chronic Studies	Page 34, 1st Para	In this paragraph, it is stated that "*Among Urea-exposed male rats, there was a significant occurrence in tumor incidence (21/50, 27/48, 25/48, and 35/50) at the high dose for interstitial adenomas in the testes(p=0.004)" …."Since the change in the incidence of malignant lymphoma occurrence did not show a dose response these results were considered by the authors to be of questionable biological significance."* We agree that the absence of a dose-response effect for lymphomas suggests that these are of limited significance. However, it is interesting to note that in other IRIS assessments the finding of a significant trend and a statistically significant	The quality control procedures for producing IRIS documents should ensure that animal bioassay results are given similar interpretations for every chemical assessment within the same time frame. When substantial differences in interpretation are made due to changes in understanding of the results, these should be noted.	O

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			difference between control and the highest dose (the response of which did not change in the reanalysis) have been used previously as both demonstrations of carcinogenicity and for a linear extrapolation to low doses.		
9	4.2.1.2 Chronic Studies	Page 34, 1st Para	The text states: *"(There is a discrepancy in Fleischman et al (1980) between the table providing the data and the narrative"*. Given that the dissimilar results were from a National Cancer Institute (NCI) study, perhaps the issue could have been resolved by contacting the NCI.	As part of its review process, EPA should consider resolving issues concerning studies from other Federal agencies.	O
10	4.6.1 Oral Exposure	70	The information of this section would be enhanced and put in perspective if it included information on urea being an endogenous product of protein catabolism. This additional information would inform the reader that organisms have homeostatic mechanism by which physiologic concentrations of urea are regulated and that humans excrete 20-30 grams per day via the urine.	Include information on urea being an endogenous product of protein catabolism and that organisms have homeostatic mechanisms by which physiologic concentrations of urea are regulated and that the dose of urea required for toxicity would need to be sufficient to upset these physiologic mechanisms.	S