USE OF THE BENCHMARK DOSE APPROACH IN CARCINOGENIC RISK ASSESSMENT FOR 4-(METHYLNITROSAMINO)-1-(3-PYRIDYL)-1-BUTANONE (NNK)

Ashley R. Turner and Felix Ayala-Fierro
ITG Brands LLC, Greensboro, NC

ABSTRACT

The Benchmark Dose (BMD) approach for Carcinogen Risk Assessment was implemented by modeling tumor data and exposure to establish a dose-response relationship. The aim of the study to compare Inhalation Unit Risk (IUR) values from scientific literature for NNK (Nicotine-derived nitrosamine ketone) using the BMDS to establish an appropriate IUR for regulatory submissions. First, the IUR was derived using linear extrapolation and then a benchmark dose lower bound (BMDL1.0) was established as the Point of Departure (POD). The Lifetime Average Daily Intake (LADI, Exposure Concentration) was calculated for NNK in two commercial cigarette products under ISO and HCI smoking conditions and converted to daily doses. The excess cancer risk was calculated as the Incremental Lifetime Cancer Risk (ILCR) and compared to the IUR and POD.

The maximum exposure levels, under HCI smoking conditions, resulted in exposures approximately 1/10th the IUR and below the POD. The difference in excess cancer risk in the two products was very small. At ISO smoking conditions exposure levels were approximately 1/20th the IUR and also below POD. There was a slight difference in excess cancer risk between the two products but the change in this region of the dose-response curve indicates no impact to human health. Margin-of-Exposure (MOE) for NNK were calculated at the BMDL1.0 and compared to literature values. At the BMDL1.0 the MOE could be interpreted as the Margin-of-Safety (MOS). The use of the POD as the reference for health effects can be expanded to other analytes with debatable IURs published by different agencies or in the public literature.

Summary BMD Modeling Results from Rivenson Publication

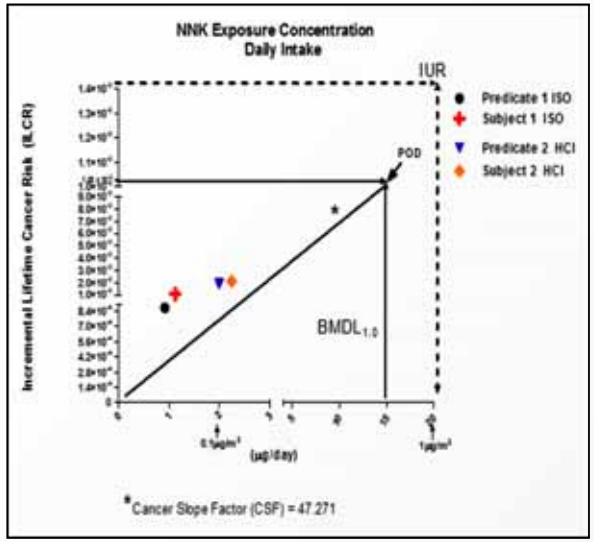
Model	BMR*	BMD (mg/kg-day)	BMDL (mg/kg-day)	p-value	AIC	Scaled Residual
Multistate Degree 1	10%	0.003027	0.002217	0.0616	274.63102	-1.52478732
Multistate Degree 1	1%	0.000289	0.000212	0.0616	274.63102	0.536250989
Multistate Degree 1	0.1%	0.0000287	0.000021	0.0616	274.63102	0.536250989

* Benchmark Response

Summary BMD Modeling Results from Naufal Publication

Model	BMR	BMD (mg/kg-day)	BMDL (mg/kg-day)	p-value	AIC	Scaled Residual
Multistate Degree 1 (Lungs)	10%	0.007686	0.004909	0.374746	193.6841	-0.730033539
Multistate Degree 2 (Lungs)	10%	0.009807	0.0005237	Not Given	194.8688	$-4.25101E^{-7}$
Multistate Degree 1 (Pancreas)	10%	0.013398	0.008212	0.853847	108.4654	-0.095011943
Multistate Degree 2 (Pancreas)	10%	0.013398	0.008213	0.853847	108.4654	-0.95012037

FIGURE 1



4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) Exposure Concentration vs. Incremental Lifetime Cancer Risk (ILCR).

INTRODUCTION

The Benchmark Dose (BMD) approach is a widely accepted method using dose-response modeling to obtain doses correlating to specific responses; near the lower dose range based on observed data recommended by the USEPA's Guidelines for Carcinogen Risk Assessment. The lower 95% confidence is used as the default point of departure (POD) to estimate the reference concentration (RfC) or cancer slope factor (CSF) and is generally considered to be conservatively protective of public health, including sensitive populations.

The BMD approach and linear extrapolation to low doses were used, as per the USEPA guidelines, for assessing the NNK cancer risk based on data from the Rivenson study after allometric scaling and route-to-route extrapolation. Ideally, peer reviewed literature is used to develop toxicodynamic models for selecting an appropriate response level to establish toxicity reference values including CSF. The CSF is then used to derive the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to 1 µg/m^3 in air (IUR).

The comparison of the ILCR to the NNK IUR and POD allows to determine the extent of the risk to make risk management decisions. Any difference in risk between two products below the POD is anticipated to be undistinguishable and therefore both products could be considered equivalent.

Development of Cancer Slope Factor and Inhalation Unit Risk for NNK

Model	BMR	BMDL (mg/kg-day)	CSF (mg/kg-day)$^{-1}$	Unit Risk (µg/m^3)$^{-1}$
Multistate Degree 1	10%	0.000212	47.271	0.014
Multistate Degree 1 (Lungs)*	1%	0.004909	20.371	0.006
Multistate Degree 1 / 2 (Pancreas)*	0.1%	0.005237	19.096	0.005

* Naufal Publication

BMDL as the POD for Dose and Exposure Reference Values

Model	BMR	POD (µg/kg-day)	Dose (µg/day)	Exposure (µg/m^3)
Naufal	10%	5.2*	364	18.2
CBI/ITGB	1%	0.212	14.84	0.742

*Lungs only

CONCLUSIONS

The Rivenson's NNK study in rats, cited for toxicological critical effects, was reviewed by CalEPA and Naufal *et al* (2009) resulting in different CSF and IUR values. ITGB implemented a conservative cancer risk through the linear model approach, generally considered to be protective of public health, following USEPA guidelines. The oral CSF using a BMDL1.0 was calculated using the BMD software for all tumors in the lung, nasal cavity, pancreas, and liver. Based on this approach ITGB currently believes that the IUR of 0.014 (µg/m^3)$^{-1}$ (CalEPA) is a better estimate for the purpose of risk assessment. ITGB's BMD approach resulted in a BMDL1.0 of 0.212 µg/kg/day (14.84 µg/day or ~0.742 µg/m^3) used as the POD and reference for the estimated exposure values. This POD value is lower than the established NNK IUR and corresponded to an ILCR of 1.03E-02.

ITGB also reviewed additional scientific publications and determined Margin-of-Exposure and calculated BMDL$_{1.0}$; these values indicate ample margins to further support the assessment that these products do not raise any different questions of public health when comparing two products (Figure 1).

Rivenson, A., et al., 1988. Induction of lung and exocrine pancreas tumours in F344 rats by tobacco-specific and Areca-derived N-nitrosamines. Cancer Research 48: 6912-6917.
Naufal, Z., Kathman, S., & Wilson, C. (2009). Bayesian derivation of an oral cancer slope factor distribution for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Regulatory Toxicology and Pharmacology, 55(1), 69-75.
EPA, U. About Benchmark Dose Software (BMDS) Retrieved February 4, 2019, from https://www.epa.gov/bmds/about-benchmark-dose-software-bmds#methods